



Animal and cellular models of chronic pain

Lili X. Wang, Zaijie Jim Wang*

Department of Biopharmaceutical Sciences, University of Illinois, 833 South Woods Street, Chicago, IL 60612, USA

Received 7 April 2003; accepted 8 May 2003

Abstract

Chronic pain, especially neuropathic pain and cancer pain, is often not adequately treated by currently available analgesics. Animal models provide pivotal systems for preclinical study of pain. This article reviews some of the most widely used or promising new models for chronic pain. Partial spinal ligation, chronic constriction injury, and L5/L6 spinal nerve ligation represent three of the best characterized rodent models of peripheral neuropathy. Recently, several mouse and rat bone cancer pain models have been reported. Primary or permanent cultures of sensory neurons have been established to study the molecular mechanism of pain, especially for neurotransmitter release and signal transduction. The emerging gene microarray, genomics and proteomics methods may be applied to thoroughly characterize these cells. Each model is uniquely created with distinct mechanisms, it is therefore essential to report and interpret results in the context of a specific model. © 2003 Elsevier B.V. All rights reserved.

Keywords: Allodynia; Hyperalgesia; Cancer; Neuropathy; Nerve injury; Sensory neurons

Contents

1. Introduction	950
2. Models of neuropathic pain	950
2.1. Central pain models	951
2.1.1. Weight-drop or contusion model (Allen technique)	951
2.1.2. Photochemical SCI model	952
2.1.3. Excitotoxic spinal cord injury (ESCI)	952
2.2. Peripheral nerve injury models	952
2.2.1. Neuroma model	952
2.2.2. Chronic constriction injury model (CCI or Bennett model)	952
2.2.3. Partial sciatic nerve ligation model (PSL or Seltzer model)	952
2.2.4. L5/L6 spinal nerve ligation model (SNL)	953
2.2.5. L5 spinal nerve ligation	953
2.2.6. Sciatic cryoneurolysis model (SCN)	953
2.2.7. Inferior caudal trunk resection model (ICTR)	954
2.2.8. Sciatic inflammatory neuritis model (SIN)	954
3. Peripheral neuropathy induced by diseases	954

*Corresponding author. Tel.: +1-312-996-0888; fax: +1-312-996-0098.

E-mail address: zjwang@uic.edu (Z.J. Wang).

3.1. Postherpetic neuralgia model (PHN).....	954
3.2. Diabetic neuropathic pain model (DNP)	954
4. Cancer pain models	954
4.1. Chemotherapy-induced peripheral neuropathy models.....	955
4.1.1. Vincristine-induced peripheral neuropathy model (VIPN)	955
4.1.2. Taxol-induced peripheral neuropathy model (TIPN)	955
4.1.3. Cisplatin-induced peripheral neuropathy model (CIPN)	955
4.2. Cancer invasion pain model (CIP).....	955
4.3. Bone cancer pain models	956
4.3.1. Mouse femur bone cancer pain model (FBC)	956
4.3.2. Mouse calcaneus bone cancer pain (CBC)	956
4.3.3. Rat tibia bone cancer model (TBC)	956
5. Cellular models	956
5.1. Primary culture of sensory neurons.....	956
5.2. Permanent sensory neuron cultures.....	957
5.2.1. Immortalized sensory cells by fusion	957
5.2.2. Immortalized sensory cells by transformation	957
6. Conclusions	957
Acknowledgements	958
References	958

1. Introduction

Pain, an unpleasant sensation that we all experience in daily life, is an alert mechanism to prevent further or impending tissue injury. Acute pain rarely needs medical attention; when it does, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, more powerful opioid analgesics, or local anesthetics can adequately control the pain. Almost all currently used analgesics were initially developed for acute pain.

Chronic pain differs from acute pain not only in its onset and duration, but more importantly in the underlying mechanisms. Chronic pain may not have identifiable ongoing injury or inflammation, and often responds poorly to NSAIDs and opioids. Better treatment of chronic pain will require clear understanding of what leads to such persistent pain, and testing of pharmacological agents in such settings. Animal models can provide useful and essential systems to study chronic pain. Numerous animal models have been developed to simulate specific human painful conditions, mostly by producing diseases or traumatic injuries that have painful sequelae.

Neuropathic pain and cancer pain are two of the most difficult types of pain to treat, and are the focus of this review. Pain can be studied in primates [1–3] and other mammals [4–7], but rodent models are by

far the most widely used. Studying pain mechanisms in cell lines is still an expanding area; however, a number of studies have demonstrated the power of such models in elucidating the molecular mechanism of neurotransmitter release and signal transduction in pain.

2. Models of neuropathic pain

Neuropathic pain refers to pain as a result of damage (due to injury or disease) to the nervous system including nerves, spinal cord and certain CNS regions [8,9]. Patients with neuropathic pain often suffer from spontaneous pain, allodynia (pain response to normally innocuous stimuli), and hyperalgesia (aggravated pain evoked by noxious stimuli) (Table 1). Neuropathic pain can have delayed onset after initial nerve injury; therefore, pain may be present in the absence of detectable lesion or injury, making proper diagnosis and early treatment difficult. In addition, neuropathic pain may spread beyond cutaneous distribution of injured nerves and exist bilaterally in mirror image sites, suggesting the involvement of a central mechanism [10,11]. Patients often describe their pain as having a burning, shooting, electric shock, or piercing quality.

Although causalgia was observed and first reported as early as the 19th century [12], mechanisms

Table 1
Characteristics of human neuropathic pain

Spontaneous pain
Allodynia
Hyperalgesia
Long lasting: months, years, even for life
Delayed onset: pain may be present without ongoing injury or pathology
Quality of pain: burning, stabbing, shooting, electric shock, piercing, etc.
Distribution: pain may spread beyond the cutaneous distribution of injured nerve
pain may exist bilaterally in mirror image sites

underlying neuropathic pain have not been extensively studied until very recently. Progress has been largely accelerated by the availability of clinically-relevant animal models to study these painful conditions. Most neuropathic pain models are made by producing diseases or causing injuries to the spinal cord or peripheral nerves. Several of the most commonly used models are described in this review, although numerous other models have also been reported [13–18].

Whereas the testing methods and models for acute pain may be useful for study of chronic pain, the latter has its unique tests and indices (Table 2). Direct evaluation of spontaneous pain in animals is

Table 2
Behavioral tests for the study of chronic pain

<i>Spontaneous pain</i>
Posture
Avoiding weight bearing on the injured side
Gait
Limping of the affected limb
Nocifensive signs
Paw licking
Excessive grooming
Excessive exploratory behavior
Guarding of the affected limb
Autotomy [20]
Self-mutilation and attack of denervated areas
<i>Allodynia</i>
Tactile allodynia (e.g. von Frey filament [213])
Cold allodynia [80,83]
<i>Hyperalgesia</i>
Thermal hyperalgesia
Radiant heat test (e.g. Hargreaves's test [214])
Hot-plate
Mechanical hyperalgesia
(e.g. Randall-Selitto paw pressure device [215]
von Frey filament)

not possible. Instead, signs of paw guarding, lifting, and limping, excessive grooming and biting, changes in exploratory behavior, weight bearing, and autotomy (see below) have been suggested as indications for the presence of spontaneous pain [19–23]. In addition, evoked pain (allodynia and thermal hyperalgesia) to thermal or mechanical stimuli can be observed in animal models, although not all are detectable in some models.

2.1. Central pain models

A number of central pain models have been reported in the literature; most are based on spinal cord injury (SCI). Dysesthesia is one of the major life style-altering changes that SCI patients have to cope with in addition to other physical challenges [24–27]. Both spontaneous and evoked pain are frequent sequelae of traumatic or ischemic spinal cord injury. Animal models of SCI include weight dropping [28], spinal cord compression [29–31], crushing of spinal cord with forceps or aneurysm [32–34], photochemically induced injury, excitatory neurotoxin methods, and spinal hemisection [35–39].

2.1.1. Weight-drop or contusion model (Allen technique)

The weight-drop model is the oldest and most widely used SCI model, although its recent use has decreased. SCI is produced by dropping a weight on the surgically exposed spinal dorsal surface at the lower thoracic-lumbar level [28,40,41]. This experimental model results in severe paraplegia and development of complete segmental necrosis. Modifications have been made to provide better control of the degree of SCI [4,42].

2.1.2. Photochemical SCI model

The photochemical model uses an intravenous photosensitizing dye, erythrosin B, which, upon excitation by an argon ion laser at the exposed vertebrate location, produces vessel occlusion and subsequent parenchymal tissue damage at the endothelial surface of spinal cord vessels [43–45]. Following such spinal ischemic event, autotomy, mechanical and cold allodynia, and hyperalgesia are observed in animals [45–47].

2.1.3. Excitotoxic spinal cord injury (ESCI)

Significant neurochemical changes occur after spinal cord injury [27,48]. Intraspinal injection of some of these neurochemicals can produce abnormal pain mimicking SCI-induced pain in humans. The best studied ESCI model is that of quisqualic acid (QUIS), an AMPA-metabotropic receptor agonist [49]. Intraspinal injection of QUIS can produce long-lasting spontaneous pain (excessive grooming), mechanical allodynia and thermal hyperalgesia in rats [50,51]. Further studies show that QUIS is able to induce neuronal loss in specific regions of spinal gray matter, but spares the superficial laminae of dorsal horn neurons [27,51,52]. Using different injection depths and doses, graded neuronal loss and pain behavior can be obtained [51]. This SCI pain model has been used by other research groups [e.g., 53] and can also be reproduced in mice [54].

Other excitatory amino acid (e.g. glutamate, *N*-methyl-D-aspartic acid, kainic acid) [55–58], dynorphin A(1–17), des-Tyr-dynorphin A peptides [54,59,60], serotonin and tryptamine [61], and other agents have also been reported to produce SCI-related pain behaviors when injected either intraspinally or intrathecally.

2.2. Peripheral nerve injury models

Peripheral neuropathic pain is a complex syndrome resulting from damage to the peripheral nervous system due to trauma, compression, neurotoxins, infection, immune and metabolic diseases, tumors, vitamin deficiencies, and other causes. A number of animal models have been reported to simulate human peripheral neuropathic conditions, most of which are based on procedures at or near sciatic nerves. Methods differ in the location and

form of injury. The latter includes transection [20], loose [62] or tight [63] ligation, cryoneurolysis [21], crush [64,65], perineural inflammation [66], and tumor invasion [67].

2.2.1. Neuroma model

Total sciatic nerve transection and ligation at multiple levels has been reported to study clinical conditions such as amputation [20]. Following complete nerve transection at multiple locations along the sciatic nerve of rats and mice, a neuroma develops at the proximal nerve stump, consisting of regenerative nerves sprouting in all directions [68–70]. Wall et al. [20] observed self-attack and mutilation of the denervated limb by injured animals, and used the term ‘autotomy’ to describe the behavior that is probably caused by complete nerve deafferentation of a limb [71,72]. Although somewhat controversial, the presence of autotomy is generally considered a sign of spontaneous pain [73–76]. The extent of autotomy depends on the method and location of neurectomy [77]. Ethical considerations may also be an issue when animals demonstrate excessive autotomy [78,79]. In a neuroma model, allodynia and hyperalgesia, the characteristic symptoms of peripheral neuropathy, can not be detected [80].

2.2.2. Chronic constriction injury model (CCI or Bennett model)

Bennett and Xie reported a rat model of painful peripheral mononeuropathy in 1988. The model loosely ties the sciatic nerve (left or right side) with four chronic gut ligatures at the mid-thigh level [80]. CCI rats show behavioral signs of spontaneous pain such as mild to moderate autotomy, guarding, excessive licking and limping of ipsilateral hind paw, and avoidance of placing weight on the injury side. Hyperalgesia due to noxious thermal and mechanical stimuli is detectable, as are cold allodynia and tactile allodynia [80,81]. All pain signs last for the entire duration of the study (over 2 months).

2.2.3. Partial sciatic nerve ligation model (PSL or Seltzer model)

In an attempt to simulate causalgia as a result of partial nerve injury in humans, Seltzer and colleagues reported a rat model of neuropathic pain in 1990 [62]. The experimental procedure involves the

ligation of the ipsilateral sciatic nerve at the high-thigh level, so that 1/3–1/2 thickness of the sciatic nerve is trapped in the ligature. PNL rats exhibit signs of allodynia to von Frey hair stimulation and hyperalgesia to both thermal and mechano-noxious stimuli within hours of ligation; the symptoms last for over 7 months. Ligated rats also display signs of spontaneous pain in the forms of paw guarding and licking on the injury side. The evoked pain can develop into bilateral patterns [62].

2.2.4. L5/L6 spinal nerve ligation model (SNL)

Kim and Chung reported in 1992 another experimental mononeuropathy model simulating human causalgia [63,82]. In the SNL, L5 and L6 spinal nerves are unilaterally and tightly ligated at a location distal to the dorsal root ganglia. Allodynia and hyperalgesia develop quickly after ligation, and last for at least 4 months. Although there are behavioral signs of spontaneous pain (guarding, licking, and lifting of ipsilateral hind paw), autotomy is absent in the SNL.

Compared to CCI and PSL, the ligation site and extent (i.e. complete ligation) are more consistent in SNL [83,84]. SNL also has the advantage of having separate injured and intact spinal segments. On the other hand, SNL requires the most extensive surgical procedures of the three models. CCI, PSL and SNL can all be produced in mice [85–87] and are the three most widely used peripheral neuropathy models. A recent Medline search yields hundreds of citations using one of these methods. A comparison of these three models is summarized in Table 3.

2.2.5. L5 spinal nerve ligation

When the L5/L6 ligation model was first reported, ligation of L4 or L5 spinal nerve was also reported. Ligation of L4 spinal nerve is not a useful pain model as it causes severe motor deficit and interferes with behavioral tests since it has an abundance of motor fibers [63]. The L5 ligation model has not been fully characterized; however, L5-ligated rats also exhibited long lasting hyperalgesia and mechanical allodynia [63]. Since single L5 nerve ligation is much easier to perform than the L5/L6 ligation, this model may provide a useful option, especially in studies involving mice (e.g. gene knockout or transgenic mice) [54]. It should be noted that as the term ‘Chung model’ can mean either L5 or L5/L6 spinal nerve ligation [63], the exact procedure should be explained in publications.

2.2.6. Sciatic cryoneurolysis model (SCN)

Instead of complete transection or ligation, freezing of the sciatic nerve has been used to produce nerve injury in the SCN model [21,88]. Autotomy and touch allodynia are present after SCN. Ligation, transection or cryoneurolysis models showed little difference in pain behaviors in the first 7 days after injury [89]. One potential advantage of this method is that cryoneurolysis-induced nerve injury may be reversible, thus offering an opportunity to study the effect of transient nerve injury and the healing process [90,91]. Indeed, SCN-induced autotomy, spontaneous nociceptive behaviors and touch-evoked allodynia lasted only 15–21 days, in contrast to the much longer duration of pain behaviors in SNL, PSL and CCI models [21].

Table 3
Comparison of three peripheral neuropathic pain models

Model ^a	Spontaneous pain ^b	Autotomy	Mechanical allodynia ^b	Cold ^b allodynia	Thermal hyperalgesia	Mechanical hyperalgesia	Bilateral
CCI	+++	+	+	+++	+	+	±
PSL	++	±	++	++	+	+	+
SNL	+	-	+++	+	+	+	+

^a CCI, chronic constriction injury model [80,81]; PSL, partial sciatic nerve ligation model [62]; SNL, L5/L6 spinal nerve ligation model [63]. The onset of pain for all three models is within hours to 1 day. The duration of pain is over weeks, but may vary somewhat in different studies and among tests [62,80,81,83,84].

^b +++: Largest; ++: moderate; +: smallest when compared for the same index among three models; data are from [83,84]. Otherwise, +: present; ±: present, but mild; -: absent.

2.2.7. Inferior caudal trunk resection model (ICTR)

The model is performed by unilaterally resecting the inferior caudal trunk between S3 and S4 nerves [92,93]. The ICTR model is interesting since it allows behavioral tests to be performed at the tail, instead of the hindpaw. Testing on the tail is easier and more consistent as the test location can be fixed by marking. Even more importantly, the ICTR model does not lead to deformity of the tail or paw limping, so true blind-testing is possible. Mechanical allodynia, and cold or thermal hyperalgesia develop within a day after injury, and can last for weeks. This model is relatively new and has not been used by other groups.

2.2.8. Sciatic inflammatory neuritis model (SIN)

It is estimated that nearly half of human neuropathies are caused by inflammation or infection rather than trauma [94,95]. In addition, inflammatory events occur after traumatic nerve injuries. Several studies have used a neuritis model to inflict nerve damage. In the SIN model, allodynia is seen hours after the injection of zymosan around the sciatic nerve, which can be bilateral at higher doses [96,97]. Thermal hyperalgesia (determined by Hargreaves' radiant heat test) cannot be detected in the SIN [96]. Peri-sciatic immune activation by placing a proinflammatory gut suture [98], dead bacteria or carrageenan [99] on the sciatic nerve can produce both allodynia and hyperalgesia.

3. Peripheral neuropathy induced by diseases

In human, shingles and diabetes are two very common diseases with neuropathic pain sequelae. Diabetes mellitus is the leading cause of neuropathy in the Western world [100]. In one series of studies, neuropathy is present in 66% of diabetic patients [101], although this prevalence is lower in another patient population [100]. Shingles is characterized by a very painful rash. Some patients suffer from postherpetic neuralgia following acute shingles, which can persist for many years and even for life.

3.1. Postherpetic neuralgia model (PHN)

Shingles is caused by reactivation of a primary infection with varicella-zoster virus. Postherpetic neuralgia (PHN) is characterized by the presence of both spontaneous and evoked pain symptoms (such as burning and aching) [102,103]. Based on the rat model of latent varicella-zoster virus infection [104,105], a recent study found persistent allodynia and hyperalgesia in infected rats, which appeared to be only on the ipsilateral, but not contralateral, hind paw [106]. Additional studies have been conducted in cells (including sensory neurons) infected with varicella-zoster virus [107–109].

3.2. Diabetic neuropathic pain model (DNP)

A few diabetic models are available, e.g. insulin deficient BB rats [110] and NOD mice [111,112], insulin resistant ob/ob and db/db mice [113–115], the Mongolian gerbil ('sand rat') [116,117], and chemically-induced models [118,119]. The most commonly used model for the study of pain is that of streptozocin-induced diabetic neuropathy model [119–122]. Streptozocin kills insulin-secreting islet cells. In rats, a single i.p. injection of streptozocin induces long lasting thermal and mechanical hyperalgesia, and cold and thermal allodynia [119–122].

4. Cancer pain models

Pain is a common symptom in cancer patients, affecting 30–50% of patients undergoing active treatment for a solid tumor and 70–90% of those with advanced diseases [123,124]. Whereas improving diagnosis and treatment methods are increasing the survival rate and life expectancy of cancer patients, cancer pain is increasingly becoming a bigger problem affecting the quality of life. Current treatment is largely based on empirical clinical experience with incomplete success. Cancer-related pain may be caused by tumor infiltration or compression of nerve, plexus, or roots, immunoreactive and pronociceptive substances released from tumors, or by treatment (chemotherapy, radiation, or surgery)

[125]. Several studies have attempted to model chemotherapy-induced peripheral neuropathy. Recently, three rodent models of bone cancer pain have been reported.

4.1. Chemotherapy-induced peripheral neuropathy models

Peripheral neuropathy and bone marrow suppression are two very frequent and severe side-effects of chemotherapy and are often the limiting factors for achieving effective doses. Neurotoxicity is particular problematic for vinca alkaloids, platinum compounds, and Taxols, although other chemotherapeutic agents are also capable of inducing neuropathy. Chemotherapy-induced neuropathy may continue after the cessation of therapy (called ‘coasting’) [216]. When administered to animals, these chemicals also produce neuropathy which may be used to study causes, prevention and treatment of their neurotoxicity.

4.1.1. Vincristine-induced peripheral neuropathy model (VIPN)

Vincristine, a vinca alkaloid, is given to treat acute leukemia, neuroblastoma, Kaposi’s sarcoma, Hodgkin’s disease and other lymphomas. It binds to tubulin and blocks microtubule polymerization, thus arresting mitosis in metaphase. Severe peripheral neuropathy occurs as a result of vincristine treatment and is a limiting factor for dose escalation which often is needed to achieve the desired anti-tumor effect. Several methods have been described to induce pain by vincristine. In rats, daily injection of vincristine for 10 days (5 consecutive drug days + 2 drug-free days + 5 more drug days) produces hyperalgesia [126,127]. A similar model produces mechanical hyperalgesia and allodynia, and a loss of sensitivity (thermal hypoalgesia) in rats [128]. Continuous intravenous vincristine infusion can also result in dose-dependent tactile allodynia, but no thermal hyperalgesia can be detected [129]. The reason why different treatments with vincristine can produce either hyperalgesia or allodynia, or both, remains to be clarified.

4.1.2. Taxol-induced peripheral neuropathy model (TIPN)

Paclitaxel (Taxol) is an antineoplastic agent derived from the Pacific yew tree *Taxus brevifolia* and is used to treat a variety of cancers, including ovarian and breast tumors, and non-small cell lung cancer [130–132]. Taxol binds to tubulin (at a site different from that used by the vinca alkaloids) and blocks polymerization of microtubules. Its effectiveness is limited by the development of severe painful peripheral neuropathy that is dose-dependent [133–135]. The incidence of Taxol neuropathy is estimated to be 50–90%, and is characterized by dysesthesia (e.g. numbness, tingling and burning pain) of the hands and feet [130,131,134,136]. A number of rat or mouse models of Taxol-induced neuropathic pain have been reported [134,137–142]. Both allodynia and thermal hyperalgesia can be detected in Taxol-treated animals.

4.1.3. Cisplatin-induced peripheral neuropathy model (CIPN)

Cisplatin is used to treat ovarian and small cell lung cancer. Cisplatin induces polyneuropathy that is dose- and treatment duration-dependent, and can last for over 10 years [143]. It has been suggested that cisplatin-induced apoptosis may contribute to its neurotoxicity [144,145]. Repeated daily injections (i.p.) of cisplatin produce mechanical allodynia and hyperalgesia [146]. Similar observations have been reported in other CIPN models [140,147,148]. These models have been used to test a number of experimental treatments that may be useful to alleviate cisplatin neuropathy [149–155].

4.2. Cancer invasion pain model (CIP)

Peripheral nerve injury and neuritis models can be used to simulate peripheral nerve damage due to cancer invasion. A more direct way to study the compression and infiltration of peripheral nerves by tumors was reported recently [67]. When Meth A sarcoma cells were implanted around the sciatic nerve in BALB/c mice, these animals developed signs of allodynia and thermal hyperalgesia as the tumor grew and compressed the nerve. Signs of spontaneous pain (paw lifting) were also visible.

This model may have the advantage of producing gradual but progressive damage to the nerve. Interestingly, mechanical allodynia (measured by von Frey filaments) could initially be observed (day 10), but the CIP-mice reverted to mechanical hyposensitivity on day 14. In cancer patients, pain may be present with sensory loss in the affected area [156,157].

4.3. Bone cancer pain models

Bone cancer pain is one of the most common cancer-related pains [158–160]. Bone cancer can be primary or metastatic from breast, prostate, ovary and lung tumors [158]. Deep pain with a burning and stabbing sensation is often described by bone cancer patients [159,160]. Three bone cancer pain models have been reported in the past 3 years; more cancer pain models will likely follow in the coming years.

4.3.1. Mouse femur bone cancer pain model (FBC)

In this model, osteolytic mouse sarcoma NCTC2472 cells are used to induce bone cancer by injecting tumor cells into the marrow space of the femur bone and sealing the injection site [161]. For histocompatibility, C3H/HeJ mice are used for this model. Within 5 days of sarcoma injection, cancer-induced bone destruction and osteoclastogenesis begin. Signs of spontaneous (nocifensive behavior, spontaneous flinching) and evoked pain (palpation-evoked flinching), as well as changes in neurochemical markers occur within 14 days [162,163], and can be attenuated by osteoprotegerin [164,165]. Opioids and cyclooxygenase (COX)-2 inhibitors are also capable of reversing pain in this model [166–168]. Further studies using this model suggest that cancer pain is different from typical inflammatory or neuropathic pain, as it affects a unique set of neurochemical markers that share many similarities with human cancer induced bone pain [167–169].

4.3.2. Mouse calcaneus bone cancer pain (CBC)

The CBC model is similar to the FBC model, except that NCTC2472 cells are injected into mouse calcaneus bone [170]. Osteolysis, spontaneous pain (paw licking) and evoked pain (mechanical and cold allodynia) occur 6 days after implantation and last

for at least 16 days. Longer observation, and tests using other stimuli have not been reported. The development of spontaneous activity and sensitization to heat in C-fibers correlate with the growth of tumor in the first 2 weeks [171]. Intraplantar administration of ET-A receptor antagonist BQ-123 can partially block tumor-associated mechanical hyperalgesia in the CBC model [170].

4.3.3. Rat tibia bone cancer model (TBC)

In the TBC model, MRMT-1 rat mammary gland carcinoma cells are injected into the tibia bone of Sprague–Dawley rats [172]. Bone destruction can be detected within 10 days of tumor cell injection. The onset of allodynia and mechanical hyperalgesia are dose (tumor cell number)-dependent, and occur within 10–12 days of tumor cell injection. Chronic treatment with zoledronic acid, but not pamidronate or the selective COX-2 inhibitor celebrex, attenuated mechanical allodynia and hyperalgesia. The effect of COX2 inhibitor in the TBC model is different from that in the mouse FBC model [166], suggesting that different bone cancer models may have different underlying mechanisms based on animal species, tumor type and location. Intravenous pamidronate has been shown to be effective in reducing the onset of skeletal complications and attenuating pain in patients with osteolytic metastases due to breast cancer and multiple myeloma [173].

5. Cellular models

Cell lines are useful for studying the molecular and cellular mechanisms of both acute and chronic pain. When applying appropriate stimuli (e.g. ‘pain-mediator chemicals’, low pH, heat) and relevant measurement endpoints, cellular models may mimic certain aspects of *in vivo* signal transduction between cells or within a single cell. Most studies have utilized primary sensory neurons, which can be harvested from naive or injured animals. Permanent cell lines are also available.

5.1. Primary culture of sensory neurons

Sensory neurons can be isolated and cultured *in vitro* from different animal species [174,175]. The

most widely used protocols use sensory neurons isolated from the neonatal [175–177] and embryonic [178,179] rat. Trigeminal and dorsal root ganglion sensory neurons in culture exhibit certain characteristics of those in vivo. These cells respond to capsaicin, bradykinin, substance P and prostaglandin applied in the culture [175,179–181], showing properties similar to those of in vivo sensory neurons [182,183]. It is not known if gene and protein expression, especially those related to the sensory functions, are altered during the culture or by serum or other chemicals in the media (e.g. nerve growth factor). Nevertheless, these cultures have been found to be valuable for studying pain neurotransmitter release [178,184,185], elucidating signal transduction [186–189], and identifying cell surface pain mediators [190–195]. Sensory neurons can be isolated not only from naive animals, but also from animals that have been treated with drugs or subjected to nerve injury [194,196,197]. Nerve terminals can even be injected with DiIC18 before sacrificing the animals, so cells can be identified in culture for in vivo–in vitro correlation and comparison [177,191].

5.2. Permanent sensory neuron cultures

Whereas primary cultures of sensory neurons exhibit many of the innate properties of these neurons, the disadvantage of primary cultures include laborious isolation procedures, limited cell numbers, and heterogeneity of the primary culture. There have been studies to establish permanent cell lines that have the properties of endogenous sensory cells. In general, two methods are used to immortalize neuronal cells: (i) viral or particular oncogene transformation; and (ii) fusion of neurons with other immortalized cell lines.

5.2.1. Immortalized sensory cells by fusion

F-11 [198,199] and ND [200] cell lines are created by fusing mouse N18Tg2 neuroblastoma cells with postmitotic embryonic or adult dorsal root ganglia sensory neurons, respectively. These cells are selected and established because of the presence of neuronal markers and properties that are unique to the parental rat sensory neurons [198–200]. F-11 and ND cells have been used to study responses to substance P, bradykinin, capsaicin, opioids, and

prostaglandins, and downstream signaling events [194,201–204]. Expression of other genes may be induced by various differentiation conditions [190,205]. However, these cells also have drawbacks such as properties that belong to parental neuroblastoma N18Tg2 cells.

5.2.2. Immortalized sensory cells by transformation

A permanent sensory cell line has been established by immortalizing human embryonic sensory neurons from dorsal root ganglia with a retroviral vector containing *v-myc* oncogene [206]. A selected clonal cell line HD10.6 exhibits characteristics similar to those of small-diameter TrkA-positive sensory neurons [206]. These include sensory neuron-specific transcription factors, immunoreactivity to substance P and TrkA, responses to capsaicin and a P2X receptor agonist. Notably missing are the tetrodotoxin (TTX)-resistant sodium channels, which are expressed in sensory neurons in vivo [207], as the entire current is TTX-sensitive in HD10.6 cells [206]. Overall, the preliminary results from the HD10.6 cells are very promising. This cell line may be of great value for the study of cellular mechanisms pertaining to pain and its treatment.

6. Conclusions

Studies employing animal models, especially those closely simulating certain clinical painful conditions, have markedly improved our knowledge of pain and its underlying mechanisms. In the next few years, it is almost certain that more animal models will become available.

Data from different models should be reported and interpreted in the context of the specific pain model. Although there may be common underlying mechanisms in many chronic pain conditions (e.g. central sensitization [208]), different models also have their own specific underlying mechanisms. In the clinic, different pain syndromes can be observed in patients even with very similar injuries or diseases [25,26].

Although most rat models of chronic pain can be reproduced in mice, different species respond to the same injury or disease differently. Similarly, age and strain difference can affect the results [209–212], and therefore strain and the commercial source of the

animals should also be taken into consideration when comparing results from different studies.

Although cultures of sensory neurons have been reported and used for over 20 years, cellular models have not been extensively used in pain study. The major concern is that expression of various functional receptors, ion channels and neurochemicals may be changed from their native state during culturing and differentiation. With advances in DNA microarray and proteomics techniques, it is now possible to systematically compare gene and protein expression in these cells under specific growth and differentiation conditions. On the other hand, studies employing sensory cells in signal transduction and pain neurotransmitter release have clearly demonstrated the power of cell systems. Animal and cellular models are making it possible to rationally design and screen drugs specifically for chronic pain.

Acknowledgements

This work was supported by a grant from the NIH and funds from the University of Illinois.

References

- [1] M. Levitt, J.H. Levitt, The deafferentation syndrome in monkeys: dysesthesias of spinal origin, *Pain* 10 (1981) 129–147.
- [2] E.J. Kirk, D. Denny-Brown, Functional variation in dermatomes in the macaque monkey following dorsal root lesions, *J. Comp. Neurol.* 139 (1970) 307–320.
- [3] S.M. Carlton, H.A. Lekan, S.H. Kim, J.M. Chung, Behavioral manifestations of an experimental model for peripheral neuropathy produced by spinal nerve ligation in the primate, *Pain* 56 (1994) 155–166.
- [4] R.W. Ford, A reproducible spinal cord injury model in the cat, *J. Neurosurg.* 59 (1983) 268–275.
- [5] J.L. Hylden, M.A. Ruda, H. Hayashi, R. Dubner, Descending serotonergic fibers in the dorsolateral and ventral funiculi of cat spinal cord, *Neurosci. Lett.* 62 (1985) 299–304.
- [6] R.P. Yezierski, R.H. Schwartz, Response and receptive-field properties of spinomesencephalic tract cells in the cat, *J. Neurophysiol.* 55 (1986) 76–96.
- [7] T. Ogawa, Y. Mimura, H. Kato, S. Ootsubo, M. Murakoshi, The usefulness of rabbits as an animal model for the neuropathological assessment of neurotoxicity following the administration of vincristine, *Neurotoxicology* 21 (2000) 501–511.
- [8] C.J. Woolf, R.J. Mannion, Neuropathic pain: aetiology, symptoms, mechanisms, and management, *Lancet* 353 (1999) 1959–1964.
- [9] M. Zimmermann, Pathobiology of neuropathic pain, *Eur. J. Pharmacol.* 429 (2001) 23–37.
- [10] R. Dubner, Neuronal plasticity and pain following peripheral tissue inflammation or nerve injury, in: M.R. Bond, J.E. Charlton, C.J. Woolf (Eds.), *Proceedings of the VIth World Congress on Pain*, Elsevier, Amsterdam, 1991, pp. 263–276.
- [11] C.J. Woolf, Windup and central sensitization are not equivalent, *Pain* 66 (1996) 105–108.
- [12] S.W. Mitchell, *Injuries of Nerves and Their Consequence*, J.B. Lippincott, Philadelphia, PA, 1872.
- [13] H. Markus, B. Pomeranz, D. Krushelnicky, Spread of saphenous somatotopic projection map in spinal cord and hypersensitivity of the foot after chronic sciatic denervation in adult rat, *Brain Res.* 296 (1984) 27–39.
- [14] J.A. Vallin, W.S. Kingery, Adjacent neuropathic hyperalgesia in rats: a model for sympathetic independent pain, *Neurosci. Lett.* 133 (1991) 241–244.
- [15] B.H. Lee, R. Won, E.J. Baik, S.H. Lee, C.H. Moon, An animal model of neuropathic pain employing injury to the sciatic nerve branches, *Neuroreport* 11 (2000) 657–661.
- [16] M. Kawakami, J.N. Weinstein, K. Chatani, K.F. Spratt, S.T. Meller, G.F. Gebhart, Experimental lumbar radiculopathy. Behavioral and histologic changes in a model of radicular pain after spinal nerve root irritation with chronic gut ligatures in the rat, *Spine* 19 (1994) 1795–1802.
- [17] M.C. Lombard, B.S. Nashold Jr., D. Albe-Fessard, N. Salman, C. Sakr, Deafferentation hypersensitivity in the rat after dorsal rhizotomy: a possible animal model of chronic pain, *Pain* 6 (1979) 163–174.
- [18] H.B. Brinkhus, M. Zimmermann, Characteristics of spinal dorsal horn neurons after partial chronic deafferentation by dorsal root transection, *Pain* 15 (1983) 221–236.
- [19] G.J. Bennett, Neuropathic pain: new insights, new interventions, *Hosp. Pract. (Off. Ed.)* 33 (1998) 95–98, also see pp. 101–104, 107–110.
- [20] P.D. Wall, M. Devor, R. Inbal, J.W. Scadding, D. Schonfeld, Z. Seltzer, M.M. Tomkiewicz, Autotomy following peripheral nerve lesions: experimental anaesthesia dolorosa, *Pain* 7 (1979) 103–111.
- [21] J.A. DeLeo, D.W. Coombs, S. Willenbring, R.W. Colburn, C. Fromm, R. Wagner, B.B. Twitchell, Characterization of a neuropathic pain model: sciatic cryoneurolysis in the rat, *Pain* 56 (1994) 9–16.
- [22] T. Kauppila, V.K. Kontinen, A. Pertovaara, Weight bearing of the limb as a confounding factor in assessment of mechanical allodynia in the rat, *Pain* 74 (1998) 55–59.
- [23] C.D. Mills, J.J. Grady, C.E. Hulsebosch, Changes in exploratory behavior as a measure of chronic central pain following spinal cord injury, *J. Neurotrauma* 18 (2001) 1091–1105.
- [24] A. Beric, M.R. Dimitrijevic, U. Lindblom, Central dysesthesia syndrome in spinal cord injury patients, *Pain* 34 (1988) 109–116.
- [25] M.J. Cohen, Z.K. Song, S.L. Schandler, W.H. Ho, M. Vulpe,

- Sensory detection and pain thresholds in spinal cord injury patients with and without dysesthetic pain, and in chronic low back pain patients, *Somatosens. Motor Res.* 13 (1996) 29–37.
- [26] M.J. Cohen, D.L. McArthur, M. Vulpe, S.L. Schandler, K.E. Gerber, Comparing chronic pain from spinal cord injury to chronic pain of other origins, *Pain* 35 (1988) 57–63.
- [27] R.P. Yeziarski, Pain following spinal cord injury: the clinical problem and experimental studies, *Pain* 68 (1996) 185–194.
- [28] A.R. Allen, Surgery of experimental lesion of spinal cord equivalent to crush injury of fracture dislocation of spinal column, *J. Am. Med. Assoc.* 57 (1911) 878–880.
- [29] C.H. Tator, Experimental circumferential compression injury of primate spinal cord, *Proc. Veterans Adm. Spinal Cord Inj. Conf.* 18 (1971) 2–5.
- [30] I.M. Tarlov, Acute spinal cord compression paralysis, *J. Neurosurg.* 36 (1972) 10–20.
- [31] C.H. Tator, Acute spinal cord injury in primates produced by an inflatable extradural cuff, *Can. J. Surg.* 16 (1973) 222–231.
- [32] A. Bjorklund, R. Katzman, U. Stenevi, K.A. West, Development and growth of axonal sprouts from noradrenaline and 5-hydroxytryptamine neurones in the rat spinal cord, *Brain Res.* 31 (1971) 21–33.
- [33] A.S. Rivlin, C.H. Tator, Regional spinal cord blood flow in rats after severe cord trauma, *J. Neurosurg.* 49 (1978) 844–853.
- [34] A.S. Rivlin, C.H. Tator, Effect of duration of acute spinal cord compression in a new acute cord injury model in the rat, *Surg. Neurol.* 10 (1978) 38–43.
- [35] M.D. Christensen, A.W. Everhart, J.T. Pickelman, C.E. Hulsebosch, Mechanical and thermal allodynia in chronic central pain following spinal cord injury, *Pain* 68 (1996) 97–107.
- [36] A.D. Bennett, A.W. Everhart, C.E. Hulsebosch, Intrathecal administration of an NMDA or a non-NMDA receptor antagonist reduces mechanical but not thermal allodynia in a rodent model of chronic central pain after spinal cord injury, *Brain Res.* 859 (2000) 72–82.
- [37] A.D. Bennett, K.M. Chastain, C.E. Hulsebosch, Alleviation of mechanical and thermal allodynia by CGRP(8-37) in a rodent model of chronic central pain, *Pain* 86 (2000) 163–175.
- [38] M.D. Christensen, C.E. Hulsebosch, Chronic central pain after spinal cord injury, *J. Neurotrauma* 14 (1997) 517–537.
- [39] C.E. Hulsebosch, R.E. Coggeshall, Quantitation of sprouting of dorsal root axons, *Science* 213 (1981) 1020–1021.
- [40] J.D. Balentine, Pathology of experimental spinal cord trauma. I. The necrotic lesion as a function of vascular injury, *Lab. Invest.* 39 (1978) 236–253.
- [41] J. Greenberg, P.E. McKeever, J.D. Balentine, Lysosomal activity in experimental spinal cord trauma: an ultrastructural cytochemical evaluation, *Surg. Neurol.* 9 (1978) 361–364.
- [42] T.E. Anderson, A controlled pneumatic technique for experimental spinal cord contusion, *J. Neurosci. Methods* 6 (1982) 327–333.
- [43] B.D. Watson, R. Prado, W.D. Dietrich, M.D. Ginsberg, B.A. Green, Photochemically induced spinal cord injury in the rat, *Brain Res.* 367 (1986) 296–300.
- [44] R. Prado, W.D. Dietrich, B.D. Watson, M.D. Ginsberg, B.A. Green, Photochemically induced graded spinal cord infarction. Behavioral, electrophysiological, and morphological correlates, *J. Neurosurg.* 67 (1987) 745–753.
- [45] J.X. Hao, X.J. Xu, H. Aldskogius, A. Seiger, Z. Wiesenfeld-Hallin, Allodynia-like effects in rat after ischaemic spinal cord injury photochemically induced by laser irradiation, *Pain* 45 (1991) 175–185.
- [46] X.J. Xu, J.X. Hao, H. Aldskogius, A. Seiger, Z. Wiesenfeld-Hallin, Chronic pain-related syndrome in rats after ischemic spinal cord lesion: a possible animal model for pain in patients with spinal cord injury, *Pain* 48 (1992) 279–290.
- [47] J.X. Hao, X.J. Xu, H. Aldskogius, A. Seiger, Z. Wiesenfeld-Hallin, Photochemically induced transient spinal ischemia induces behavioral hypersensitivity to mechanical and cold stimuli, but not to noxious-heat stimuli, in the rat, *Exp. Neurol.* 118 (1992) 187–194.
- [48] M. Marsala, L.S. Sorkin, T.L. Yaksh, Transient spinal ischemia in rat: characterization of spinal cord blood flow, extracellular amino acid release, and concurrent histopathological damage, *J. Cereb. Blood Flow Metab.* 14 (1994) 604–614.
- [49] R.P. Yeziarski, S.H. Park, The mechanosensitivity of spinal sensory neurons following intraspinal injections of quisqualic acid in the rat, *Neurosci. Lett.* 157 (1993) 115–119.
- [50] R.P. Yeziarski, M. Santana, S.H. Park, P.W. Madsen, Neuronal degeneration and spinal cavitation following histopathological injections of quisqualic acid in the rat, *J. Neurotrauma* 10 (1993) 445–456.
- [51] R.P. Yeziarski, S. Liu, G.L. Ruenes, K.J. Kajander, K.L. Brewer, Excitotoxic spinal cord injury: behavioral and morphological characteristics of a central pain model, *Pain* 75 (1998) 141–155.
- [52] R.P. Yeziarski, Pain following spinal cord injury: pathophysiology and central mechanisms, *Prog. Brain Res.* 129 (2000) 429–449.
- [53] K.E. Abraham, J.F. McGinty, K.L. Brewer, Spinal and supraspinal changes in opioid mRNA expression are related to the onset of pain behaviors following excitotoxic spinal cord injury, *Pain* 90 (2001) 181–190.
- [54] C.A. Fairbanks, K.L. Schreiber, K.L. Brewer, C.G. Yu, L.S. Stone, K.F. Kitto, H.O. Nguyen, B.M. Grocholski, D.W. Shoeman, L.J. Kehl, S. Regunathan, D.J. Reis, R.P. Yeziarski, G.L. Wilcox, Agmatine reverses pain induced by inflammation, neuropathy, and spinal cord injury, *Proc. Natl. Acad. Sci. USA* 97 (2000) 10584–10589.
- [55] G.L. Wilcox, Pharmacological studies of grooming and scratching behavior elicited by spinal substance P and excitatory amino acids, *Ann. NY Acad. Sci.* 525 (1988) 228–236.
- [56] L.M. Aanonsen, G.L. Wilcox, Muscimol, gamma-aminobutyric acid A receptors and excitatory amino acids in the mouse spinal cord, *J. Pharmacol. Exp. Ther.* 248 (1989) 1034–1038.
- [57] X.F. Sun, A.A. Larson, Behavioral sensitization to kainic

- acid and quisqualic acid in mice: comparison to NMDA and substance P responses, *J. Neurosci.* 11 (1991) 3111–3123.
- [58] D. Budai, G.L. Wilcox, A.A. Larson, Enhancement of NMDA-evoked neuronal activity by glycine in the rat spinal cord in vivo, *Neurosci. Lett.* 135 (1992) 265–268.
- [59] T.W. Vanderah, T. Laughlin, J.M. Lashbrook, M.L. Nichols, G.L. Wilcox, M.H. Ossipov, T.P. Malan Jr., F. Porreca, Single intrathecal injections of dynorphin A or des-Tyr-dynorphins produce long-lasting allodynia in rats: blockade by MK-801 but not naloxone, *Pain* 68 (1996) 275–281.
- [60] T.M. Laughlin, T.W. Vanderah, J. Lashbrook, M.L. Nichols, M. Ossipov, F. Porreca, G.L. Wilcox, Spinally administered dynorphin A produces long-lasting allodynia: involvement of NMDA but not opioid receptors, *Pain* 72 (1997) 253–260.
- [61] A.A. Larson, G.L. Wilcox, Synergistic behavioral effects of serotonin and tryptamine injected intrathecally in mice, *Neuropharmacology* 23 (1984) 1415–1418.
- [62] Z. Seltzer, R. Dubner, Y. Shir, A novel behavioral model of neuropathic pain disorders produced in rats by partial sciatic nerve injury, *Pain* 43 (1990) 205–218.
- [63] S.H. Kim, J.M. Chung, An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat, *Pain* 50 (1992) 355–363.
- [64] M. Devor, D. Schonfeld, Z. Seltzer, P.D. Wall, Two modes of cutaneous reinnervation following peripheral nerve injury, *J. Comp. Neurol.* 185 (1979) 211–220.
- [65] I. Decosterd, A. Allchorne, C.J. Woolf, Progressive tactile hypersensitivity after a peripheral nerve crush: non-noxious mechanical stimulus-induced neuropathic pain, *Pain* 100 (2002) 155–162.
- [66] J.A. DeLeo, R.P. Yezierski, The role of neuroinflammation and neuroimmune activation in persistent pain, *Pain* 90 (2001) 1–6.
- [67] M. Shimoyama, K. Tanaka, F. Hasue, N. Shimoyama, A mouse model of neuropathic cancer pain, *Pain* 99 (2002) 167–174.
- [68] K. Fried, R. Govrin-Lippmann, F. Rosenthal, M.H. Ellisman, M. Devor, Ultrastructure of afferent axon endings in a neuroma, *J. Neurocytol.* 20 (1991) 682–701.
- [69] M. Devor, P.D. Wall, Type of sensory nerve fibre sprouting to form a neuroma, *Nature* 262 (1976) 705–708.
- [70] R. Amir, M. Devor, Ongoing activity in neuroma afferents bearing retrograde sprouts, *Brain Res.* 630 (1993) 283–288.
- [71] Z. Seltzer, Y. Paran, A. Eisen, R. Ginzburg, Neuropathic pain behavior in rats depends on the afferent input from nerve-end neuroma including histamine-sensitive C-fibers, *Neurosci. Lett.* 128 (1991) 203–206.
- [72] N.E. Saade, M.Z. Ibrahim, S.F. Atweh, S.J. Jabbur, Explosive autotomy induced by simultaneous dorsal column lesion and limb denervation: a possible model for acute deafferentation pain, *Exp. Neurol.* 119 (1993) 272–279.
- [73] B.E. Rodin, L. Kruger, Deafferentation in animals as a model for the study of pain: an alternative hypothesis, *Brain Res.* 319 (1984) 213–228.
- [74] T.J.Coderre, R.W. Grimes, R. Melzack, Deafferentation and chronic pain in animals: an evaluation of evidence suggesting autotomy is related to pain, *Pain* 26 (1986) 61–84.
- [75] T.J. Coderre, R. Melzack, Procedures which increase acute pain sensitivity also increase autotomy, *Exp. Neurol.* 92 (1986) 713–722.
- [76] T. Kauppila, Correlation between autotomy-behavior and current theories of neuropathic pain, *Neurosci. Biobehav. Rev.* 23 (1998) 111–129.
- [77] R. Zeltser, B. Beilin, R. Zaslansky, Z. Seltzer, Comparison of autotomy behavior induced in rats by various clinically-used neurectomy methods, *Pain* 89 (2000) 19–24.
- [78] B. Blumenkopf, J.J. Lipman, Studies in autotomy: its pathophysiology and usefulness as a model of chronic pain, *Pain* 45 (1991) 203–209.
- [79] J.M. Riopelle, The ethics of using animal models to study treatment of phantom pain, *Anesthesiology* 76 (1992) 1069–1071.
- [80] G.J. Bennett, Y.K. Xie, A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man, *Pain* 33 (1988) 87–107.
- [81] N. Attal, F. Jazat, V. Kayser, G. Guilbaud, Further evidence for ‘pain-related’ behaviours in a model of unilateral peripheral mononeuropathy, *Pain* 41 (1990) 235–251.
- [82] Y. Choi, Y.W. Yoon, H.S. Na, S.H. Kim, J.M. Chung, Behavioral signs of ongoing pain and cold allodynia in a rat model of neuropathic pain, *Pain* 59 (1994) 369–376.
- [83] B.H. Lee, Y.W. Yoon, K. Chung, J.M. Chung, Comparison of sympathetic sprouting in sensory ganglia in three animal models of neuropathic pain, *Exp. Brain Res.* 120 (1998) 432–438.
- [84] K.J. Kim, Y.W. Yoon, J.M. Chung, Comparison of three rodent neuropathic pain models, *Exp. Brain Res.* 113 (1997) 200–206.
- [85] A.B. Malmberg, A.I. Basbaum, Partial sciatic nerve injury in the mouse as a model of neuropathic pain: behavioral and neuroanatomical correlates, *Pain* 76 (1998) 215–222.
- [86] C. Sommer, M. Schafers, Painful mononeuropathy in C57BL/Wld mice with delayed Wallerian degeneration: differential effects of cytokine production and nerve regeneration on thermal and mechanical hypersensitivity, *Brain Res.* 784 (1998) 154–162.
- [87] Z. Wang, L.R. Gardell, M.H. Ossipov, T.W. Vanderah, M.B. Brennan, U. Hochgeschwender, V.J. Hruby, T.P. Malan Jr., J. Lai, F. Porreca, Pronociceptive actions of dynorphin maintain chronic neuropathic pain, *J. Neurosci.* 21 (2001) 1779–1786.
- [88] R. Wagner, J.A. DeLeo, D.W. Coombs, S. Willenbring, C. Fromm, Spinal dynorphin immunoreactivity increases bilaterally in a neuropathic pain model, *Brain Res.* 629 (1993) 323–326.
- [89] R.W. Colburn, A.J. Rickman, J.A. DeLeo, The effect of site and type of nerve injury on spinal glial activation and neuropathic pain behavior, *Exp. Neurol.* 157 (1999) 289–304.
- [90] S. Willenbring, I.G. Beuprie, J.A. DeLeo, Sciatic cryoneurolysis in rats: a model of sympathetically independent pain. Part I: Effects of sympathectomy, *Anesth. Analg.* 81 (1995) 544–548.
- [91] S. Willenbring, J.A. DeLeo, D.W. Coombs, Sciatic

- cryoneurolysis in rats: a model of sympathetically independent pain. Part 2: Adrenergic pharmacology, *Anesth. Analg.* 81 (1995) 549–554.
- [92] H.S. Na, J.S. Han, K.H. Ko, S.K. Hong, A behavioral model for peripheral neuropathy produced in rat's tail by inferior caudal trunk injury, *Neurosci. Lett.* 177 (1994) 50–52.
- [93] S.K. Back, B. Sung, S.K. Hong, H.S. Na, A mouse model for peripheral neuropathy produced by a partial injury of the nerve supplying the tail, *Neurosci. Lett.* 322 (2002) 153–156.
- [94] C.N. Bourque, B.A. Anderson, C. Martin del Campo, A.A. Sima, Sensorimotor perineuritis—an autoimmune disease?, *Can. J. Neurol. Sci.* 12 (1985) 129–133.
- [95] G. Said, M. Hontebeyrie-Joskowicz, Nerve lesions induced by macrophage activation, *Res. Immunol.* 143 (1992) 589–599.
- [96] M. Chacur, E.D. Milligan, L.S. Gazda, C. Armstrong, H. Wang, K.J. Tracey, S.F. Maier, L.R. Watkins, A new model of sciatic inflammatory neuritis (SIN): induction of unilateral and bilateral mechanical allodynia following acute unilateral peri-sciatic immune activation in rats, *Pain* 94 (2001) 231–244.
- [97] L.S. Gazda, E.D. Milligan, M.K. Hansen, C.M. Twining, N.M. Poulos, M. Chacur, K.A. O'Connor, C. Armstrong, S.F. Maier, L.R. Watkins, R.R. Myers, Sciatic inflammatory neuritis (SIN): behavioral allodynia is paralleled by perisciatic proinflammatory cytokine and superoxide production, *J. Peripher. Nerv. Syst.* 6 (2001) 111–129.
- [98] T.J. Maves, P.S. Pechman, G.F. Gebhart, S.T. Meller, Possible chemical contribution from chronic gut sutures produces disorders of pain sensation like those seen in man, *Pain* 54 (1993) 57–69.
- [99] E. Eliav, U. Herzberg, M.A. Ruda, G.J. Bennett, Neuropathic pain from an experimental neuritis of the rat sciatic nerve, *Pain* 83 (1999) 169–182.
- [100] Z. Simmons, E.L. Feldman, Update on diabetic neuropathy, *Curr. Opin. Neurol.* 15 (2002) 595–603.
- [101] P.J. Dyck, K.M. Kratz, J.L. Karnes, W.J. Litchy, R. Klein, J.M. Pach, D.M. Wilson, P.C. O'Brien, L.J. Melton 3rd, F.J. Service, The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study, *Neurology* 43 (1993) 817–824.
- [102] M.C. Rowbotham, G. Yosipovitch, M.K. Connolly, D. Finlay, G. Forde, H.L. Fields, Cutaneous innervation density in the allodynic form of postherpetic neuralgia, *Neurobiol. Dis.* 3 (1996) 205–214.
- [103] M.C. Rowbotham, H.L. Fields, The relationship of pain, allodynia and thermal sensation in post-herpetic neuralgia, *Brain* 119 (1996) 347–354.
- [104] C. Sadzot-Delvaux, M.P. Merville-Louis, P. Delree, P. Marc, J. Piette, G. Moonen, B. Rentier, An in vivo model of varicella-zoster virus latent infection of dorsal root ganglia, *J. Neurosci. Res.* 26 (1990) 83–89.
- [105] C. Sadzot-Delvaux, S. Debrus, A. Nikkels, J. Piette, B. Rentier, Varicella-zoster virus latency in the adult rat is a useful model for human latent infection, *Neurology* 45 (1995) S18–20.
- [106] S.M. Fleetwood-Walker, J.P. Quinn, C. Wallace, G. Blackburn-Munro, B.G. Kelly, C.E. Fiskerstrand, A.A. Nash, R.G. Dalziel, Behavioural changes in the rat following infection with varicella-zoster virus, *J. Gen. Virol.* 80 (1999) 2433–2436.
- [107] C. Bourdon-Wouters, M.P. Merville-Louis, C. Sadzot-Delvaux, P. Marc, J. Piette, P. Delree, G. Moonen, B. Rentier, Acute and persistent varicella-zoster virus infection of human and murine neuroblastoma cell lines, *J. Neurosci. Res.* 26 (1990) 90–97.
- [108] M. Kress, H. Fickenscher, Infection by human varicella-zoster virus confers norepinephrine sensitivity to sensory neurons from rat dorsal root ganglia, *FASEB J.* 15 (2001) 1037–1043.
- [109] C. Sadzot-Delvaux, P. Thonard, S. Schoonbroodt, J. Piette, B. Rentier, Varicella-zoster virus induces apoptosis in cell culture, *J. Gen. Virol.* 76 (1995) 2875–2879.
- [110] A.A. Sima, Peripheral neuropathy in the spontaneously diabetic BB-Wistar-rat. An ultrastructural study, *Acta Neuropathol.* 51 (1980) 223–227.
- [111] R. Mosseri, T. Waner, M. Shefi, E. Shafir, J. Meyerovitch, Gluconeogenesis in non-obese diabetic (NOD) mice: in vivo effects of vandadate treatment on hepatic glucose-6-phosphatase and phosphoenolpyruvate carboxykinase, *Metabolism* 49 (2000) 321–325.
- [112] G.M. Pieper, H. Mizoguchi, M. Ohsawa, J. Kamei, H. Nagase, L.F. Tseng, Decreased opioid-induced antinociception but unaltered G-protein activation in the genetic-diabetic NOD mouse, *Eur. J. Pharmacol.* 401 (2000) 375–379.
- [113] J. Meyerovitch, P. Rothenberg, Y. Shechter, S. Bonner-Weir, C.R. Kahn, Vanadate normalizes hyperglycemia in two mouse models of non-insulin-dependent diabetes mellitus, *J. Clin. Invest.* 87 (1991) 1286–1294.
- [114] N. Takeshita, I. Yamaguchi, Antinociceptive effects of morphine were different between experimental and genetic diabetes, *Pharmacol. Biochem. Behav.* 60 (1998) 889–897.
- [115] J. Kamei, M. Sodeyama, M. Ohsawa, M. Kimura, S. Tanaka, Modulation by serum glucose levels on morphine-induced antinociceptive effect in C57BL/KsJ-db/db mice, *Life Sci.* 62 (1998) L1–6.
- [116] A.L. Vincent, G.E. Rodrick, W.A. Sodeman Jr., The pathology of the Mongolian gerbil (*Meriones unguiculatus*): a review, *Lab. Anim. Sci.* 29 (1979) 645–651.
- [117] E. Shafir, S. Spielman, I. Nachliel, M. Khamaisi, H. Bar-On, E. Ziv, Treatment of diabetes with vanadium salts: general overview and amelioration of nutritionally induced diabetes in the *Psammomys obesus* gerbil, *Diabetes Metab. Res. Rev.* 17 (2001) 55–66.
- [118] J.H. Lee, D.J. Cox, D.G. Mook, R.C. McCarty, Effect of hyperglycemia on pain threshold in alloxan-diabetic rats, *Pain* 40 (1990) 105–107.
- [119] C. Courteix, M. Bardin, C. Chantelauze, J. Lavarenne, A. Eschalié, Study of the sensitivity of the diabetes-induced pain model in rats to a range of analgesics, *Pain* 57 (1994) 153–160.
- [120] L.J. Forman, S. Estilow, M. Lewis, P. Vasilenko, Streptozocin diabetes alters immunoreactive beta-endorphin

- levels and pain perception after 8 weeks in female rats, *Diabetes* 35 (1986) 1309–1313.
- [121] L. Wuarin-Bierman, G.R. Zahnd, F. Kaufmann, L. Burcklen, J. Adler, Hyperalgesia in spontaneous and experimental animal models of diabetic neuropathy, *Diabetologia* 30 (1987) 653–658.
- [122] C. Courteix, A. Eschalier, J. Lavarenne, Streptozocin-induced diabetic rats: behavioural evidence for a model of chronic pain, *Pain* 53 (1993) 81–88.
- [123] P. Lesage, R.K. Portenoy, Trends in cancer pain management, *Cancer Control* 6 (1999) 136–145.
- [124] R.K. Portenoy, P. Lesage, Management of cancer pain, *Lancet* 353 (1999) 1695–1700.
- [125] C.J. Veitch, Cancer pain: a neurological perspective, *Curr. Opin. Neurol.* 13 (2000) 649–653.
- [126] K.O. Aley, D.B. Reichling, J.D. Levine, Vincristine hyperalgesia in the rat: a model of painful vincristine neuropathy in humans, *Neuroscience* 73 (1996) 259–265.
- [127] K.D. Tanner, D.B. Reichling, J.D. Levine, Nociceptor hyper-responsiveness during vincristine-induced painful peripheral neuropathy in the rat, *J. Neurosci.* 18 (1998) 6480–6491.
- [128] N. Authier, F. Coudore, A. Eschalier, J. Fialip, Pain related behaviour during vincristine-induced neuropathy in rats, *Neuroreport* 10 (1999) 965–968.
- [129] N. Nozaki-Taguchi, S.R. Chaplan, E.S. Higuera, R.C. Ajakwe, T.L. Yaksh, Vincristine-induced allodynia in the rat, *Pain* 93 (2001) 69–76.
- [130] E.K. Rowinsky, E.A. Eisenhauer, V. Chaudhry, S.G. Arbuck, R.C. Donehower, Clinical toxicities encountered with paclitaxel (Taxol), *Semin. Oncol.* 20 (1993) 1–15.
- [131] E.K. Rowinsky, V. Chaudhry, D.R. Cornblath, R.C. Donehower, Neurotoxicity of Taxol, *J. Natl. Cancer Inst. Monogr.* 15 (1993) 107–115.
- [132] M.A. Socinski, Single-agent paclitaxel in the treatment of advanced non-small cell lung cancer, *Oncologist* 4 (1999) 408–416.
- [133] G. Cavaletti, G. Bogliun, L. Marzorati, A. Zincone, M. Marzola, N. Colombo, G. Tredici, Peripheral neurotoxicity of taxol in patients previously treated with cisplatin, *Cancer* 75 (1995) 1141–1150.
- [134] G. Cavaletti, G. Tredici, M. Braga, S. Tazzari, Experimental peripheral neuropathy induced in adult rats by repeated intraperitoneal administration of taxol, *Exp. Neurol.* 133 (1995) 64–72.
- [135] Y. Mimura, H. Kato, K. Eguchi, T. Ogawa, Schedule dependency of paclitaxel-induced neuropathy in mice: a morphological study, *Neurotoxicology* 21 (2000) 513–520.
- [136] P.H. Wiernik, E.L. Schwartz, A. Einzig, J.J. Strauman, R.B. Lipton, J.P. Dutcher, Phase I trial of taxol given as a 24-h infusion every 21 days: responses observed in metastatic melanoma, *J. Clin. Oncol.* 5 (1987) 1232–1239.
- [137] O.A. Dina, X. Chen, D. Reichling, J.D. Levine, Role of protein kinase Cepsilon and protein kinase A in a model of paclitaxel-induced painful peripheral neuropathy in the rat, *Neuroscience* 108 (2001) 507–515.
- [138] R.C. Polomano, A.J. Mannes, U.S. Clark, G.J. Bennett, A painful peripheral neuropathy in the rat produced by the chemotherapeutic drug, paclitaxel, *Pain* 94 (2001) 293–304.
- [139] N. Authier, J.P. Gillet, J. Fialip, A. Eschalier, F. Coudore, Description of a short-term Taxol-induced nociceptive neuropathy in rats, *Brain Res.* 887 (2000) 239–249.
- [140] F.M. Boyle, H.R. Wheeler, G.M. Shenfield, Amelioration of experimental cisplatin and paclitaxel neuropathy with glutamate, *J. Neurooncol.* 41 (1999) 107–116.
- [141] K.D. Cliffer, J.A. Siuciak, S.R. Carson, H.E. Radley, J.S. Park, D.R. Lewis, E. Zlotchenko, T. Nguyen, K. Garcia, J.R. Tonra, N. Stambler, J.M. Cedarbaum, S.C. Bodine, R.M. Lindsay, P.S. DiStefano, Physiological characterization of Taxol-induced large-fiber sensory neuropathy in the rat, *Ann. Neurol.* 43 (1998) 46–55.
- [142] S.C. Apfel, R.B. Lipton, J.C. Arezzo, J.A. Kessler, Nerve growth factor prevents toxic neuropathy in mice, *Ann. Neurol.* 29 (1991) 87–90.
- [143] D. Strumberg, S. Brugge, M.W. Korn, S. Koeppen, J. Ranft, G. Scheiber, C. Reiners, C. Mockel, S. Seeber, M.E. Scheulen, Evaluation of long-term toxicity in patients after cisplatin-based chemotherapy for non-seminomatous testicular cancer, *Ann. Oncol.* 13 (2002) 229–236.
- [144] S.J. Fischer, J.L. Podratz, A.J. Windebank, Nerve growth factor rescue of cisplatin neurotoxicity is mediated through the high affinity receptor: studies in PC12 cells and p75 null mouse dorsal root ganglia, *Neurosci. Lett.* 308 (2001) 1–4.
- [145] E.S. McDonald, A.J. Windebank, Cisplatin-induced apoptosis of DRG neurons involves bax redistribution and cytochrome *c* release but not fas receptor signaling, *Neurobiol. Dis.* 9 (2002) 220–233.
- [146] N. Authier, J. Fialip, A. Eschalier, F. Coudore, Assessment of allodynia and hyperalgesia after cisplatin administration to rats, *Neurosci. Lett.* 291 (2000) 73–76.
- [147] P. De Koning, J.P. Neijt, F.G. Jennekens, W.H. Gispen, Evaluation of cis-diamminedichloroplatinum (II) (cisplatin) neurotoxicity in rats, *Toxicol. Appl. Pharmacol.* 89 (1987) 81–87.
- [148] E. Verdu, J.J. Vilches, F.J. Rodriguez, D. Ceballos, A. Valero, X. Navarro, Physiological and immunohistochemical characterization of cisplatin-induced neuropathy in mice, *Muscle Nerve* 22 (1999) 329–340.
- [149] P.F. Pradat, P. Kennel, S. Naimi-Sadaoui, F. Finiels, D. Scherman, C. Orsini, P. Delaere, J. Mallet, F. Revah, Viral and non-viral gene therapy partially prevents experimental cisplatin-induced neuropathy, *Gene Ther.* 9 (2002) 1333–1337.
- [150] P. Tassler, A.L. Dellon, G.J. Lesser, S. Grossman, Utility of decompressive surgery in the prophylaxis and treatment of cisplatin neuropathy in adult rats, *J. Reconstr. Microsurg.* 16 (2000) 457–463.
- [151] M.P. ter Laak, F.P. Hamers, C.J. Kirk, W.H. Gispen, rhGGF2 protects against cisplatin-induced neuropathy in the rat, *J. Neurosci. Res.* 60 (2000) 237–244.
- [152] C.C. Verstappen, A.A. Geldof, T.J. Postma, J.J. Heimans, In vitro protection from cisplatin-induced neurotoxicity by amifostine and its metabolite WR1065, *J. Neurooncol.* 44 (1999) 1–5.

- [153] F.P. Hamers, C. Pette, B. Bravenboer, C.J. Vecht, J.P. Neijt, W.H. Gispen, Cisplatin-induced neuropathy in mature rats: effects of the melanocortin-derived peptide ORG 2766, *Cancer Chemother. Pharmacol.* 32 (1993) 162–166.
- [154] W.H. Gispen, F.P. Hamers, C.J. Vecht, F.G. Jennekens, J.P. Neyt, ACTH/MSH like peptides in the treatment of cisplatin neuropathy, *J. Steroid Biochem. Mol. Biol.* 43 (1992) 179–183.
- [155] P. de Koning, J.P. Neijt, F.G. Jennekens, W.H. Gispen, Org.2766 protects from cisplatin-induced neurotoxicity in rats, *Exp. Neurol.* 97 (1987) 746–750.
- [156] K.M. Foley, Controlling the pain of cancer, *Sci. Am.* 275 (1996) 164–165.
- [157] L.A. Martin, N.A. Hagen, Neuropathic pain in cancer patients: mechanisms, syndromes, and clinical controversies, *J. Pain Symptom Manage.* 14 (1997) 99–117.
- [158] S. Mercadante, Malignant bone pain: pathophysiology and treatment, *Pain* 69 (1997) 1–18.
- [159] R.E. Coleman, R.D. Rubens, The clinical course of bone metastases from breast cancer, *Br. J. Cancer* 55 (1987) 61–66.
- [160] R.E. Coleman, R.D. Rubens, Bone metastases and breast cancer, *Cancer Treat. Rev.* 12 (1985) 251–270.
- [161] M.J. Schwei, P. Honore, S.D. Rogers, J.L. Salak-Johnson, M.P. Finke, M.L. Ramnaraine, D.R. Clohisy, P.W. Mantyh, Neurochemical and cellular reorganization of the spinal cord in a murine model of bone cancer pain, *J. Neurosci.* 19 (1999) 10886–10897.
- [162] P. Honore, J. Schwei, S.D. Rogers, J.L. Salak-Johnson, M.P. Finke, M.L. Ramnaraine, D.R. Clohisy, P.W. Mantyh, Cellular and neurochemical remodeling of the spinal cord in bone cancer pain, *Prog. Brain Res.* 129 (2000) 389–397.
- [163] P. Honore, S.D. Rogers, M.J. Schwei, J.L. Salak-Johnson, N.M. Luger, M.C. Sabino, D.R. Clohisy, P.W. Mantyh, Murine models of inflammatory, neuropathic and cancer pain each generates a unique set of neurochemical changes in the spinal cord and sensory neurons, *Neuroscience* 98 (2000) 585–598.
- [164] P. Honore, N.M. Luger, M.A. Sabino, M.J. Schwei, S.D. Rogers, D.B. Mach, F.P. O’Keefe, M.L. Ramnaraine, D.R. Clohisy, P.W. Mantyh, Osteoprotegerin blocks bone cancer-induced skeletal destruction, skeletal pain and pain-related neurochemical reorganization of the spinal cord, *Nat. Med.* 6 (2000) 521–528.
- [165] N.M. Luger, P. Honore, M.A. Sabino, M.J. Schwei, S.D. Rogers, D.B. Mach, D.R. Clohisy, P.W. Mantyh, Osteoprotegerin diminishes advanced bone cancer pain, *Cancer Res.* 61 (2001) 4038–4047.
- [166] M.A. Sabino, J.R. Ghilardi, J.L. Jongen, C.P. Keyser, N.M. Luger, D.B. Mach, C.M. Peters, S.D. Rogers, M.J. Schwei, C. de Felipe, P.W. Mantyh, Simultaneous reduction in cancer pain, bone destruction, and tumor growth by selective inhibition of cyclooxygenase-2, *Cancer Res.* 62 (2002) 7343–7349.
- [167] N.M. Luger, M.A. Sabino, M.J. Schwei, D.B. Mach, J.D. Pomonis, C.P. Keyser, M. Rathbun, D.R. Clohisy, P. Honore, T.L. Yaksh, P.W. Mantyh, Efficacy of systemic morphine suggests a fundamental difference in the mechanisms that generate bone cancer versus inflammatory pain, *Pain* 99 (2002) 397–406.
- [168] P.W. Mantyh, D.R. Clohisy, M. Koltzenburg, S.P. Hunt, Molecular mechanisms of cancer pain, *Nat. Rev. Cancer* 2 (2002) 201–209.
- [169] P.W. Mantyh, A mechanism based understanding of cancer pain, *Pain* 96 (2002) 1–2.
- [170] P.W. Wacnik, L.J. Eikmeier, T.R. Ruggles, M.L. Ramnaraine, B.K. Walcheck, A.J. Beitz, G.L. Wilcox, Functional interactions between tumor and peripheral nerve: morphology, algogen identification, and behavioral characterization of a new murine model of cancer pain, *J. Neurosci.* 21 (2001) 9355–9366.
- [171] D.M. Cain, P.W. Wacnik, M. Turner, G. Wendelschafer-Crabb, W.R. Kennedy, G.L. Wilcox, D.A. Simone, Functional interactions between tumor and peripheral nerve: changes in excitability and morphology of primary afferent fibers in a murine model of cancer pain, *J. Neurosci.* 21 (2001) 9367–9376.
- [172] K. Walker, S.J. Medhurst, B.L. Kidd, M. Glatt, M. Bowes, S. Patel, K. McNair, A. Kesingland, J. Green, O. Chan, A.J. Fox, L.A. Urban, Disease modifying and anti-nociceptive effects of the bisphosphonate, zoledronic acid in a model of bone cancer pain, *Pain* 100 (2002) 219–229.
- [173] F. Fulfaro, A. Casuccio, C. Ticozzi, C. Ripamonti, The role of bisphosphonates in the treatment of painful metastatic bone disease: a review of phase III trials, *Pain* 78 (1998) 157–169.
- [174] M. Schultzberg, T. Ebendal, T. Hokfelt, G. Nilsson, K. Pfenninger, Substance P-like immunoreactivity in cultured spinal ganglia from chick embryos, *J. Neurocytol.* 7 (1978) 107–117.
- [175] P.I. Baccaglioni, P.G. Hogan, Some rat sensory neurons in culture express characteristics of differentiated pain sensory cells, *Proc. Natl. Acad. Sci. USA* 80 (1983) 594–598.
- [176] J.E. Adler, J.A. Kessler, I.B. Black, Development and regulation of substance P in sensory neurons in vitro, *Dev. Biol.* 102 (1984) 417–425.
- [177] S.P. Eckert, A. Taddese, E.W. McCleskey, Isolation and culture of rat sensory neurons having distinct sensory modalities, *J. Neurosci. Methods* 77 (1997) 183–190.
- [178] M.R. Vasko, W.B. Campbell, K.J. Waite, Prostaglandin E2 enhances bradykinin-stimulated release of neuropeptides from rat sensory neurons in culture, *J. Neurosci.* 14 (1994) 4987–4997.
- [179] C.M. Hingtgen, M.R. Vasko, Prostacyclin enhances the evoked-release of substance P and calcitonin gene-related peptide from rat sensory neurons, *Brain Res.* 655 (1994) 51–60.
- [180] M.D. Southall, M.R. Vasko, Prostaglandin E(2)-mediated sensitization of rat sensory neurons is not altered by nerve growth factor, *Neurosci. Lett.* 287 (2000) 33–36.
- [181] G.M. Burgess, I. Mullaney, M. McNeill, P.M. Dunn, H.P. Rang, Second messengers involved in the mechanism of action of bradykinin in sensory neurons in culture, *J. Neurosci.* 9 (1989) 3314–3325.

- [182] A.I. Basbaum, Distinct neurochemical features of acute and persistent pain, *Proc. Natl. Acad. Sci. USA* 96 (1999) 7739–7743.
- [183] J. Dodd, T.M. Jessell, Lactoseries carbohydrates specify subsets of dorsal root ganglion neurons projecting to the superficial dorsal horn of rat spinal cord, *J. Neurosci.* 5 (1985) 3278–3294.
- [184] C.M. Hingtgen, M.R. Vasko, The phosphatase inhibitor, okadaic acid, increases peptide release from rat sensory neurons in culture, *Neurosci. Lett.* 178 (1994) 135–138.
- [185] L.A. Barber, M.R. Vasko, Activation of protein kinase C augments peptide release from rat sensory neurons, *J. Neurochem.* 67 (1996) 72–80.
- [186] A.R. Evans, M.R. Vasko, G.D. Nicol, The cAMP transduction cascade mediates the PGE₂-induced inhibition of potassium currents in rat sensory neurones, *J. Physiol.* 516 (1999) 163–178.
- [187] J. Dymshitz, M.R. Vasko, Nitric oxide and cyclic guanosine 3',5'-monophosphate do not alter neuropeptide release from rat sensory neurons grown in culture, *Neuroscience* 62 (1994) 1279–1286.
- [188] D.J. Martin, D. McClelland, M.B. Herd, K.G. Sutton, M.D. Hall, K. Lee, R.D. Pinnock, R.H. Scott, Gabapentin-mediated inhibition of voltage-activated Ca²⁺ channel currents in cultured sensory neurones is dependent on culture conditions and channel subunit expression, *Neuropharmacology* 42 (2002) 353–366.
- [189] J.N. Wood, P.R. Coote, A. Minhas, I. Mullaney, M. McNeill, G.M. Burgess, Capsaicin-induced ion fluxes increase cyclic GMP but not cyclic AMP levels in rat sensory neurones in culture, *J. Neurochem.* 53 (1989) 1203–1211.
- [190] P. Banerjee, E. Berry-Kravis, D. Bonafede-Chhabra, G. Dawson, Heterologous expression of the serotonin 5-HT_{1A} receptor in neural and non-neural cell lines, *Biochem. Biophys. Res. Commun.* 192 (1993) 104–110.
- [191] P. Chaudhary, M.E. Martenson, T.K. Baumann, Vanilloid receptor expression and capsaicin excitation of rat dental primary afferent neurons, *J. Dent. Res.* 80 (2001) 1518–1523.
- [192] J.N. Wood, J. Winter, I.F. James, H.P. Rang, J. Yeats, S. Bevan, Capsaicin-induced ion fluxes in dorsal root ganglion cells in culture, *J. Neurosci.* 8 (1988) 3208–3220.
- [193] J.J. Chen, J. Dymshitz, M.R. Vasko, Regulation of opioid receptors in rat sensory neurons in culture, *Mol. Pharmacol.* 51 (1997) 666–673.
- [194] J.A. Smith, S.M. Amagasa, R.M. Eglén, J.C. Hunter, K.R. Bley, Characterization of prostanoid receptor-evoked responses in rat sensory neurones, *Br. J. Pharmacol.* 124 (1998) 513–523.
- [195] T.M. Perney, L.D. Hirning, S.E. Leeman, R.J. Miller, Multiple calcium channels mediate neurotransmitter release from peripheral neurons, *Proc. Natl. Acad. Sci. USA* 83 (1986) 6656–6659.
- [196] C.J. Woolf, M.L. Reynolds, C. Molander, C. O'Brien, R.M. Lindsay, L.I. Benowitz, The growth-associated protein GAP-43 appears in dorsal root ganglion cells and in the dorsal horn of the rat spinal cord following peripheral nerve injury, *Neuroscience* 34 (1990) 465–478.
- [197] M. Petersen, J. Zhang, J.M. Zhang, R.H. LaMotte, Abnormal spontaneous activity and responses to norepinephrine in dissociated dorsal root ganglion cells after chronic nerve constriction, *Pain* 67 (1996) 391–397.
- [198] D. Platika, M.H. Boulos, L. Baizer, M.C. Fishman, Neuronal traits of clonal cell lines derived by fusion of dorsal root ganglia neurons with neuroblastoma cells, *Proc. Natl. Acad. Sci. USA* 82 (1985) 3499–3503.
- [199] D. Platika, L. Baizer, M.C. Fishman, Sensory neurons 'immortalized' by fusion with neuroblastoma cells, *Trans. Assoc. Am. Physicians* 98 (1985) 301–304.
- [200] J.N. Wood, S.J. Bevan, P.R. Coote, P.M. Dunn, A. Harmar, P. Hogan, D.S. Latchman, C. Morrison, G. Rougon, M. Theveniau et al., Novel cell lines display properties of nociceptive sensory neurons, *Proc. R. Soc. Lond. B Biol. Sci.* 241 (1990) 187–194.
- [201] P.C. Francel, K. Harris, M. Smith, M.C. Fishman, G. Dawson, R.J. Miller, Neurochemical characteristics of a novel dorsal root ganglion × neuroblastoma hybrid cell line, F-11, *J. Neurochem.* 48 (1987) 1624–1631.
- [202] K. Kusano, H. Gainer, Modulation of voltage-activated Ca currents by pain-inducing agents in a dorsal root ganglion neuronal line, F-11, *J. Neurosci. Res.* 34 (1993) 158–169.
- [203] K. Naruse, D.S. McGehee, G.S. Oxford, Differential responses of Ca-activated K channels to bradykinin in sensory neurons and F-11 cells, *Am. J. Physiol.* 262 (1992) C453–460.
- [204] S.F. Fan, K.F. Shen, M.A. Scheideler, S.M. Crain, F11 neuroblastoma × DRG neuron hybrid cells express inhibitory mu- and delta-opioid receptors which increase voltage-dependent K⁺ currents upon activation, *Brain Res.* 590 (1992) 329–333.
- [205] J.K. Singh, Q. Yan, G. Dawson, P. Banerjee, Cell-specific regulation of the stably expressed serotonin 5-HT_{1A} receptor and altered ganglioside synthesis, *Biochim. Biophys. Acta* 1310 (1996) 201–211.
- [206] H.K. Raymon, S. Thode, J. Zhou, G.C. Friedman, J.R. Pardinas, C. Barrere, R.M. Johnson, D.W. Sah, Immortalized human dorsal root ganglion cells differentiate into neurons with nociceptive properties, *J. Neurosci.* 19 (1999) 5420–5428.
- [207] J.M. Laird, V. Souslova, J.N. Wood, F. Cervero, Deficits in visceral pain and referred hyperalgesia in Nav1.8 (SNS/PN3)-null mice, *J. Neurosci.* 22 (2002) 8352–8356.
- [208] C.J. Woolf, Evidence for a central component of post-injury pain hypersensitivity, *Nature* 306 (1983) 686–688.
- [209] Y. Shir, R. Zeltser, J.J. Vatine, G. Carmi, I. Belfer, A. Zangen, D. Overstreet, P. Raber, Z. Seltzer, Correlation of intact sensibility and neuropathic pain-related behaviors in eight inbred and outbred rat strains and selection lines, *Pain* 90 (2001) 75–82.
- [210] C.D. Mills, S.D. Fullwood, C.E. Hulsebosch, Changes in metabotropic glutamate receptor expression following spinal cord injury, *Exp. Neurol.* 170 (2001) 244–257.
- [211] K.O. Aley, J.D. Levine, Different peripheral mechanisms mediate enhanced nociception in metabolic/toxic and traumatic painful peripheral neuropathies in the rat, *Neuroscience* 111 (2002) 389–397.

- [212] Y.I. Kim, H.S. Na, Y.W. Yoon, S.H. Nahm, K.H. Ko, S.K. Hong, Mechanical allodynia is more strongly manifested in older rats in an experimental model of peripheral neuropathy, *Neurosci. Lett.* 199 (1995) 158–160.
- [213] S.R. Chaplan, F.W. Bach, J.W. Pogrel, J.M. Chung, T.L. Yaksh, Quantitative assessment of tactile allodynia in the rat paw, *J. Neurosci. Methods* 53 (1994) 55–63.
- [214] K. Hargreaves, R. Dubner, F. Brown, C. Flores, J. Joris, A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia, *Pain* 32 (1988) 77–88.
- [215] L.O. Randall, J.J. Selitto, A method for measurement of analgesic activity on inflamed tissue, *Arch. Int. Pharmacodyn.* 61 (1957) 409–419.
- [216] S. Quasthoff, H.P. Hartung, Chemotherapy-induced peripheral neuropathy, *J. Neurol.* 249 (2002) 9–17.