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Review

Neuropathic pain models in the development of analgesic drugs

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ABSTRACT

Introduction: Animal disease models are predictive for signs seen in disease. They may rarely mimic all signs in a specific disease in humans with respect to etiology, cause or development. Several models have been developed for different pain states and the alteration of behavior has been interpreted as a response to external stimulus or expression of pain or discomfort. Considerable attention must be paid not to interpret other effects such as somnolence or motor impairment as a pain response and similarly not to misinterpret the response of analgesics.

Neuropathic pain is caused by injury or disease of the somatosensory system. The clinical manifestations of neuropathic pain vary including both stimulus-evoked and non-stimulus evoked (spontaneous) symptoms. By pharmacological intervention, the threshold for allodynia and hyperalgesia in the various pain modalities can be modulated and measured in animals and humans. Animal models have been found most valuable in studies on neuropathic pain and its treatment.

Aim of the study: With these interpretation problems in mind, the present text aims to describe the most frequently used animal models of neuropathic pain induced by mechanical nerve injury.

Methods: The technical surgical performance of these models is described as well as pain behavior based on the authors own experience and from a literature survey.

Results: Nerve injury in the hind limb of rats and mice is frequently used in neuropathic pain models and the different types of lesion may afford difference in the spread and quality of the pain provoked. The most frequently used models are presented, with special focus on the spared nerve injury (SNI) and the spinal nerve ligation/transection (SNL/SNT) models, which are extensively used and validated in rats and mice. Measures of mechanical and thermal hypersensitivity with von Frey filaments and Hargreaves test, respectively, are described and shown in figures.

Conclusions: A number of animal models have been developed and described for neuropathic pain showing predictive value in parallel for both humans and animals. On the other hand, there are still large knowledge gaps in the pathophysiologic mechanisms for the development, maintenance and progression of the neuropathic pain syndrome.

Implications: Better understanding of pathogenic mechanisms of neuropathic pain in animal models may support the search for new treatment paradigms in patients with complex neuropathic pain conditions.

Contents

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Abbreviations: CCI, chronic constriction injury; PSNI, partial sciatic nerve injury; SNI, spared nerve injury; SNL, spinal nerve ligation; SNT, spinal nerve transection.

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1. Introduction

The study of drug effects is initially performed in animals as models. Besides studies in healthy animals, these models are created by surgical or chemical lesions of the tissue or specific cells, by stressors to cause mental disorders or in recent years by knock-in or knock-out of specific genes in order to mimic the disease. Although, the natural origin, causes and progression of the disease are much more complex and do rarely rely on a single entity as developed and validated in animal models. Therefore, the disease models created in animals are mostly models of specific signs and not of a chronic condition. The characteristic symptoms of the modeled disease can be observed and quantified and the treatments that are developed aim to reduce these signs. This implies that most of the animal models are not able to interact with or alter the natural history of the disease, i.e. its progression. Specific models are valid, however, and are frequently used in studies on therapy of pain. Such animal models have been developed for both acute and chronic pain of different origins and the corresponding behavior of the animal has been studied. The behavior does not necessarily constitute a reaction to pain but is nevertheless used as an indicator of pain and as a response to measure the effect of analgesic drugs. Attention should be paid to alternative reasons for the behavior, e.g. obvious motor impairment, novelty seeking, fear, distress, somnolence and altered, but not painful, sensation.

Neuropathic pain is caused by injury or disease of the somatosensory system [1]. The pain may be due to a primary insult to the peripheral and/or central nervous system. The clinical manifestations of neuropathic pain vary including both stimulus-evoked and non-stimulus evoked (spontaneous) symptoms. Key features of the former are *hyperalgesia*, i.e. an increased response, or a decreased threshold, to a normal painful stimulus and *allodynia*, i.e. pain elicited by normal non-painful stimuli. By pharmacological intervention, the threshold for allodynia and hyperalgesia in the various pain modalities as e.g. mechanical, heat and cold pain can be modulated and measured in animals and humans, whereas the spontaneous pain is difficult to measure in animals and consequently it is also difficult to find treatment paradigms in this type of pain.

The spontaneous symptoms are described by some patients as shooting, lancinating or burning pain. Primary hallmarks also include *hypoesthesia* and *anesthesia*, i.e. reduced and blocked sensation, respectively. Furthermore, *dysesthesia*, which is an unpleasant abnormal sensation that can be either spontaneous or evoked, is a common symptom in neuropathic pain [2,3]. The underlying mechanisms may expand during the disease to indicate both peripheral and central pathology. Such spread of pain-generating mechanisms is due to biochemical changes of the nervous system [4]. The overall result of neuropathic pain is that, through peripheral and central sensitization, low-intensity stimulation and even activation of the structure of the nervous system normally involved in tactile sense, leads to a potentially intense, painful sensation.

Despite the presence of a genetically well-defined neuropathic pain condition like *erythromelalgia* (i.e. neuropathy characterized by pain and redness of the extremities which is aggravated by warmth) [5] and the rising understanding of genetic disposition promoting the development of neuropathic pain [6], there is currently no treatment to prevent the development of neuropathic pain. The existing pharmacological treatment alternatives to alleviate the pain are often associated with poor efficacy and intolerable side effects [7,8]. Thus, there is an unmet clinical need and a challenge to develop more effective therapies for the management of neuropathic pain. Better mechanistic understanding of existing models as well as research on the influence of genetics on the behavior of animals in models for neuropathic pain are warranted.

This present text aims to describe the most frequently used animal models of neuropathic pain. All models that are presented here involve a mechanical nerve injury. The spared nerve injury (SNI) and spinal nerve ligation/transection (SNL/SNT) models (Table 1 and Fig. 1), which are validated and extensively used in rats and mice in our facilities, are discussed in detail, whereas methods that employ chemical destruction by injecting e.g. zymosan or the cytotoxic vincristine [9] are not further discussed.

2. Animal models of neuropathic pain

An animal model is useful for research because it has specific characteristics that resemble a human disease or disorder. These characteristics can either be spontaneous or induced.

Although the knowledge about the underlying mechanisms for neuropathic pain in humans is still incomplete, a number of animal models of peripheral nerve injury might simulate human neuropathic pain signs, e.g. hyperalgesia, allodynia-like behavior and spontaneous pain, making these animal models valuable tools for neuropathic pain experiments [10]. The existing animal models are differentiated by both location and form of injury, as presented in Fig. 1. Some of the most used animal models are summarized in Table 1.

Several animal models for nerve damage and the subsequent neuropathic pain have been developed over the last decades. Here, focus is on the SNI and the SNL/SNT models, which are validated and extensively performed in rats and mice in our own facilities as well as by others. While the SNI model is relatively easy to perform and yields a high response rate, the SNL/SNT models offer advantages in that injured and intact spinal segments are separated within the dorsal root ganglion, thus allowing investigation of the relevance of input from injured and uninjured afferents in neuropathic pain for e.g. biochemical and histological examinations [10–12]. On the other hand, these models are more invasive than the other models, making the surgeries more delicate and time consuming.

Animal models using ligation can be difficult to reproduce, as the ligatures must have consistent tightness to ensure identical and uniform injury. This particularly pertains the chronic constriction injury (CCI) model [11,13], that normally requires more experience, as up to four ligatures need to be placed around the sciatic nerve.

The duration of pain response to thermal as well as mechanical pain stimuli persisted over several weeks and the magnitude of response were similar in the commonly applied animal models for neuropathic pain shown in Fig. 1 [14,15]. Distinct and robust mechanical response regarding duration and magnitude was observed in the SNI as well as the SNT model in the study presented in Fig. 2 (in-house, unpublished data).

2.1. Spared nerve injury

The SNI model was developed by Decosterd and Woolf [16]. An incision is made at the lateral surface of the left thigh, and the proximal and distal parts of the biceps femoris muscle are separated to expose the sciatic nerve and its three terminal branches. The tibial and common peroneal nerves are tightly ligated and 2–3 mm of

Table 1
Overview of frequently used animal models of neuropathic pain.

Animal model	Abbreviation	Method	Reference
Spared nerve injury	SNI	Axotomisation of the tibial and common peroneal nerves, sparing the sural nerve.	[16]
Spinal nerve ligation	SNL	Tight ligation of the L5 ± L6 spinal nerves.	[20]
Spinal nerve transection	SNT	Transection of the L5 ± L6 spinal nerves.	[28]
Chronic constriction injury	CCI	Four loose ligatures around the sciatic nerve.	[10]
Partial sciatic nerve injury	PSNI	Ligation of 1/3–1/2 of the sciatic nerve.	[31]

the nerves distal to the ligation removed. Any stretching or contact with the spared sural nerve should be avoided. The model affords high reproducibility. It is easy and fast to perform with a high operation success rate even for inexperienced operators. The SNI-operated animals have normal food intake, movements, grooming and growth [16].

Following SNI surgery, both rats and mice as early as two to three days after injury will develop long-term hypersensitivity to mechanical (Fig. 2), but not to thermal stimuli (Fig. 3) [17,18]. For rats, the hypersensitivity is of long duration (15 months or longer) [19]. For mice, the duration is at least 30 days [18]. An increased sensitivity to cold stimuli has also been observed in SNI-operated rats [16,19].

A disadvantage associated with the lesions in the peroneal and the tibial nerves leaving the sural nerve intact is that the procedure causes a degeneration of axons, which also limits the number of distal intact axons. Hence it will lead to difficulties in the performance of behavioral tests, as the ipsilateral paw includes uninjured areas close to the denervated areas [11,16]. An additional complication for the assessment of pain behavior in SNI animals is that the hypersensitive area in the limb is the lateral part of the paw that is technically difficult to test.

2.2. Spinal nerve ligation

The SNL model is associated with development of long-term hypersensitivity to mechanical and cold stimuli as well as spontaneous pain-like behavior. These behaviors develop quickly after ligation [20,21]. The development of heat hypersensitivity is more variable and not found in all experimental conditions.

The original version of the SNL model, developed by Kim and Chung, involved a tight ligation of both the L5 and L6 spinal nerves [20]. An incision is made along the spinal column and the left paraspinal muscles are separated from the spinous processes at

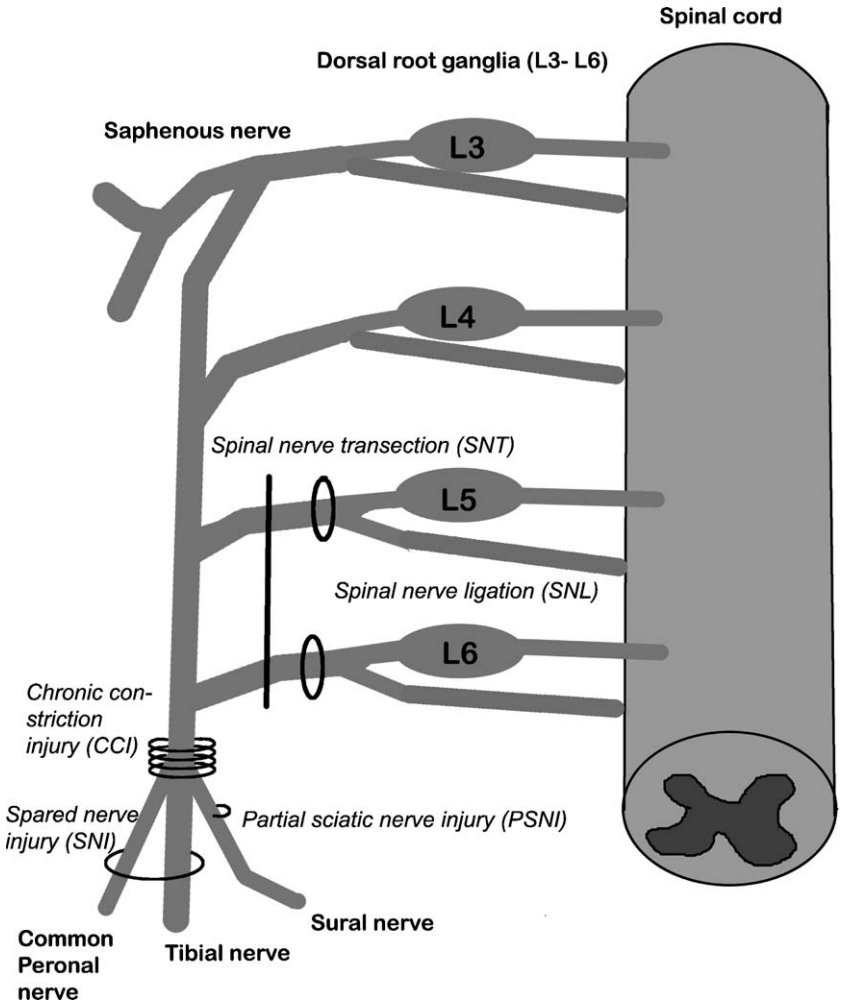

Fig. 1. Injury positions for generation of animal models of neuropathic pain. (A) Spared nerve injury, SNI [16], (B) spinal nerve ligation, SNL [20], (C) spinal nerve transection, SNT [28], (D) chronic constriction injury, CCI [10] and (E) partial sciatic nerve injury, PSNI [31].

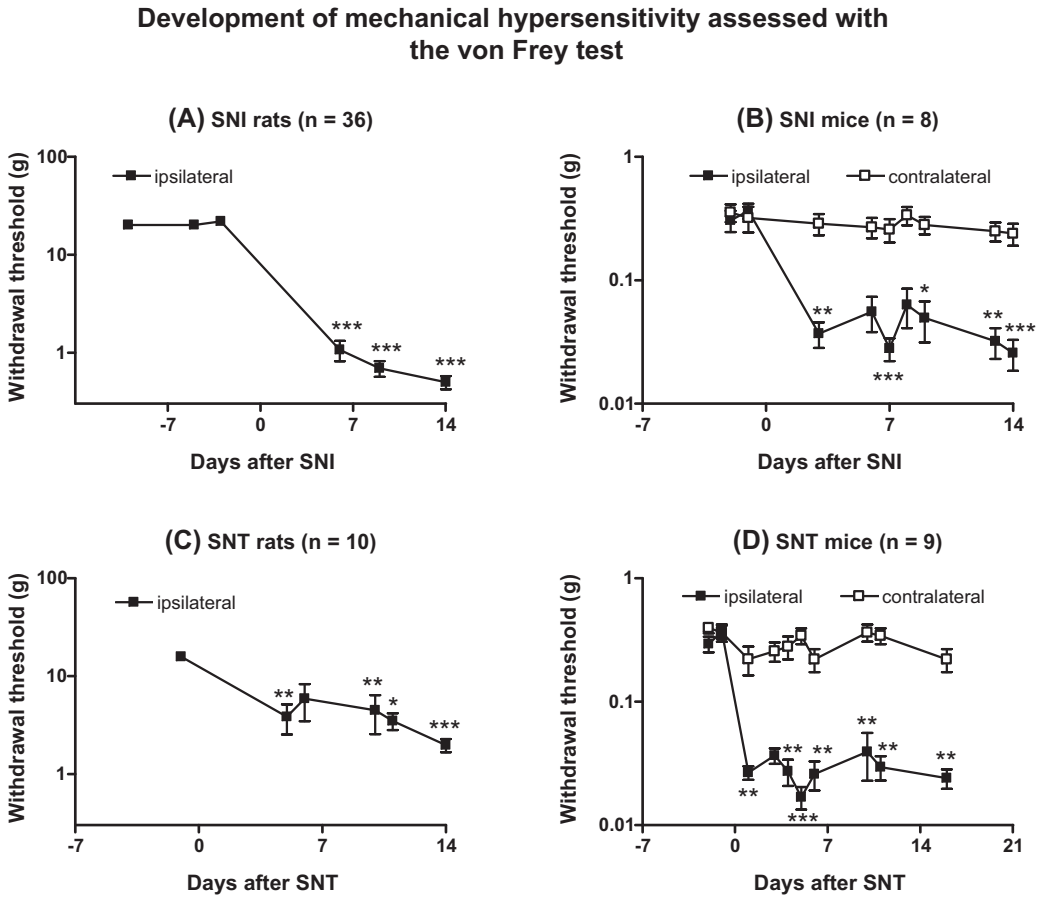

Fig. 2. Paw withdrawal threshold in response to mechanical stimulation before and after nerve injury, assessed in (A) SNI rats ($n = 36$), (B) SNI mice ($n = 8$), (C) SNT rats ($n = 10$) and (D) SNT mice ($n = 9$). The test was conducted two or three times before SNI/SNT surgery and repeatedly up to 21 days after surgery, using a set of calibrated von Frey monofilaments (Stoelting, Wood Dale, IL, USA). The bending force of the filaments, expressed in grams (g), ranged from 0.008 to 0.6 g in mouse experiments and 0.02–26 g in rat experiments, respectively. The filaments were applied to the lateral plantar surface of the hind paw in ascending order, and response threshold was the bending force of the first filament in the series that produced three withdrawals after five consecutive stimulations. If there was no response to the stiffest filament, threshold was recorded as 0.6 g for mice and 26 g for rats, respectively. Post-surgery thresholds ipsilateral to nerve injury were significantly lower than pre-surgery thresholds in both models as well as in both species ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$; Friedman repeated measures one-way ANOVA with Dunn's multiple comparison test), as opposed to contralateral thresholds (only assessed in mice) (in-house, unpublished data).

the L4-S2 levels. Under a modular high-performance stereomicroscope, the L5 spinal nerve is isolated and 1–3 mm of the nerve is ligated distal to the dorsal root ganglia. Special care should be taken to avoid any damage to the L4 spinal nerve. Based on findings that only 0.4% of all sciatic afferents resides in the L6 dorsal root ganglions [22], the surgical procedure nowadays often involves an injury only to the L5 spinal nerve. Several studies have confirmed that this modification has a very limited effect on the outcome [20,23,24]. Since then the SNL model has also been used in mice with similar characteristics as seen in rats [25].

The behavioral signs resulting from SNL surgery, e.g. guarding, licking and lifting of the ipsilateral paw, may indicate clinical face validity. Hyperalgesia, allodynia-like behavior and spontaneous pain suggest high validity, as these symptoms may be present in patients with neuropathic pain. Compared to other models, the SNL model is not associated with autotomy, i.e. scratching and biting of the denervated hind paw. A likely explanation is that the hind paws still are innervated in the SNL model and that the sensation is not only spared but exaggerated. In contrast, in the CCI and SNI model, the hind limb or part of it is denervated and entirely insensate [12,26].

An interesting observation in the SNL model is that glutamate uptake was reduced by 72% in the ipsilateral dorsal horn, in comparison to sham operated rats six weeks after surgery. This was due to suppression of the excitatory amino acid transporters and/or functions and might be a common mechanism for sensitization regardless animal model, as SNL, SNT as well as CCI all lead to definitive decrease in expression and function of this transporter [27].

2.3. Spinal nerve transection

The SNT model was originally developed as a continuation and validation of the SNL model. Apparently, the SNT model produces similar results as did the SNL model (Figs. 2 and 3). Sheen and Chung [28] could subsequently conclude that the SNT model resembles the SNL model, and can be used as an animal model for neuropathic pain as well [28]. However, it has been suggested that this model lacks the local inflammatory component that is present in the CCI, partial sciatic nerve injury (PSNI) and SNL models [27,29].

As in the SNL model, an incision is made along the spinal column and the left paraspinal muscles are separated from the spinal processes at the L4-S2 levels. Under a modular high-performance stereomicroscope, the L5 spinal nerve is isolated and 1–3 mm of the nerve is excised distal to the dorsal root ganglia.

2.4. Chronic constriction injury

A chronic painful peripheral neuropathy develops after CCI surgery due to a peripheral inflammatory reaction in response

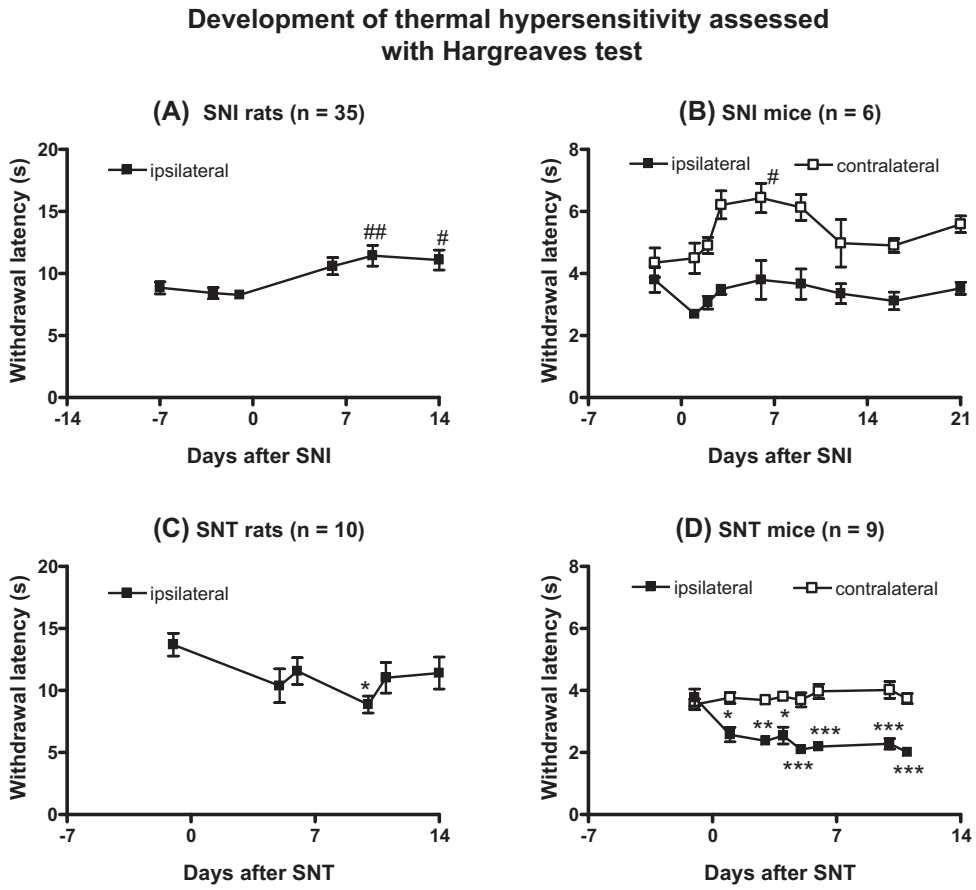

Fig. 3. Paw withdrawal latency in response to thermal stimulation before and after nerve injury, assessed in (A). SNI rats ($n = 35$), (B) SNI mice ($n = 6$), (C) SNT rats ($n = 10$) and (D) SNT mice ($n = 9$). The Hargreave's plantar test (IITC Life Sciences, Woodland Hills, CA, USA) was conducted two or three times before SNI/SNT surgery and repeatedly up to 21 days after surgery. A radiant heat source, adjusted to give a pre-surgery withdrawal latency of 4–5 s and 8–9 s for mice and rats respectively, was directed to the lateral plantar surface of the hind paw. Measurements were done by manually starting and stopping the heat source, while the time was simultaneously recorded to the nearest 0.01 s by the apparatus. Measuring of thermal stimulation demand equal and stable skin temperature of area subjected for measurement [33]. This is ensured by performing the measurement at a set ambient temperature and where the paw has contact with the glass plate. The withdrawal latency was calculated as the mean of two or three measurements, which were separated by 5 min. To prevent tissue damage, a cut-off of 20 s was used. Post-surgery latencies ipsilateral to nerve injury were significantly lower than pre-surgery latencies in the SNT model ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$; repeated measures one-way ANOVA with Bonferroni's multiple comparison test). However, in the SNI model, post-surgical latencies were either not altered or slightly higher than pre-surgery latencies ($^{\#}p < 0.05$, $^{\#\#}p < 0.01$; repeated measures one-way ANOVA with Bonferroni's multiple comparison test) (in-house, unpublished data).

to the ligatures. This is followed by a loss of most of the large myelinated Aβ-fibres, some myelinated Aδ-fibres and some small non-myelinated C-fibres [13]. Mixed signs of neuropathic pain and inflammatory components make the CCI model closest to mimicking neuropathic pain in humans [29]. The sciatic nerve receives input from L4, L5 and L6, which means that CCI affects a wider range of lumbar spinal cord levels, than does the more proximal SNT or SNL of L5 [27]. Thus, by affecting a wider range of lumbar spinal cord levels using CCI, it may result in a greater neurochemical and metabolic response than those in e.g. SNT [27]. CCI also leads to the development of allodynia-like behavior, hyperalgesia and spontaneous pain-like behaviors, which normally reach maximum 10-14 days after surgery [10–13]. CCI-operated animals develop allodynia-like behavior to cold and mechanical stimuli, and variable thermal hyperalgesia [30].

2.5. Partial sciatic nerve injury

In the PSNI model, allodynia-like behavior and hyperalgesia last for up to seven months [11,12,31]. In comparison to CCI, the PSNI model is associated with less inflammatory components [11]. Following injury, the animal develops a guarding behavior of the injured hind limb suggesting the possibility of spontaneous pain. Allodynia-like behavior to mechanical stimuli as well as thermal hyperalgesia and bilateral mechanical hyperalgesia are also developed [30].

A disadvantage concerning PSNI is the fact that an undefined number of neurons is ligated, making it complicated to relate the injury to a specific dorsal root ganglion [11]. However, this may be considered an advantage, as injury induced by PSNI might simulate neuropathic pain in humans where several dorsal root ganglions are included.

3. The use of animals models in the development of drug therapy for neuropathic pain

The majority of active drug tested in neuropathic pain have parallel outcome in clinical pain states as well as in the animal models used to express pain signs [14,15].

An array of working principles of the drugs from traditional analgesics such as opioids, prostaglandin inhibitors, drugs increasing transmitter release, different types of sodium or calcium channel blockers, excitatory amino acid modulators, cytokine receptor blockers and different neurotrophins have been used with effect in animal models of neuropathic pain. Clinical trials of those drugs tested in patients have also shown an overall pharmacological sensitivity between 61 and 81% [13,32]. This suggests that the animal

models may have value in the development of new drugs for the management, or treatment, of neuropathic pain.

A successful drug trial in animals does not always predict a clinically useful effect. First, the nature, cause and progression of a nerve lesion and degeneration are more complex than a simple ligation. The progression of the nerve damage as well as induced protective biochemical mechanisms may change with time and is probably not always the same as in the animal models. Second, an important difference is that most animals in a pharmacologic test respond to the given drug. In the clinic only a few patients respond and adverse effects might be a limitation for positive response at higher doses. Therefore, animal models may only be indicative and a search for more adequate and sensitive monitoring of adverse effects in the animal models is highly warranted as well. Third, it is still uncertain whether spontaneous pain, a serious problem in patients, is present in the animal models. There are still no validated tools or methods to measure spontaneous pain in the animal and consequently, it is not possible to evaluate any pharmacologic effect on this type of pain.

Although the animal models used may have predictive value in studies on new analgesic drug entities for treatment of neuropathic pain symptoms in patients, there are still much knowledge to be gained in the pathophysiologic mechanisms for the development of the pain syndrome, its maintenance and progression.

Implications: Better understanding of pathogenic mechanisms of neuropathic pain in animal models may support the search for new treatment paradigms in patients with complex neuropathic pain conditions.

Conflict of interest

All authors declare that they have no conflicts of interest.

References

[1] Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008;70:1630–5.

[2] Jensen TS, Baron R. Translation of symptoms and signs into mechanisms in neuropathic pain. Pain 2003;102:1–8.

[3] Baron R. Neuropathic pain: a clinical perspective. Handb Exp Pharmacol 2009:3–30.

[4] Zimmermann M. Pathobiology of neuropathic pain. Eur J Pharmacol 2001;429:23–37.

[5] Harty TP, Dib-Hajj SD, Tyrrell L, Blackman R, Hisama FM, Rose JB, Waxman SG. Na(V)1.7 mutant A863P in erythromelalgia: effects of altered activation and steady-state inactivation on excitability of nociceptive dorsal root ganglion neurons. J Neurosci 2006;26:12566–75.

[6] Tegeder I, Costigan M, Griffin RS, Abele A, Belfer I, Schmidt H, Ehnert C, Nejim J, Marian C, Scholz J, Wu T, Allchorne A, Diatchenko L, Binshtok AM, Goldman D, Adolph J, Sama S, Atlas SJ, Carlezon WA, Parsegian A, Lotsch J, Fillingim RB, Maixner W, Geisslinger G, Max MB, Woolf CJ. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat Med 2006;12:1269–77.

[7] Attal N, Cruccu G, Haanpaa M, Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 2006;13:1153–69.

[8] Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC, Wallace MS. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007;132:237–51.

[9] Nozaki-Taguchi N, Chaplan SR, Higuera ES, Ajakwe RC, Yaksh TL. Vincristine-induced allodynia in the rat. Pain 2001;93:69–76.

[10] Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain 1988;33:87–107.

[11] Bridges D, Thompson SW, Rice AS. Mechanisms of neuropathic pain. Br J Anaesth 2001;87:12–26.

[12] Wang LX, Wang ZJ. Animal and cellular models of chronic pain. Adv Drug Deliv Rev 2003;55:949–65.

[13] Hogan Q. Animal pain models. Reg Anesth Pain Med 2002;27:385–401.

[14] Kim KJ, Yoon YW, Chung JM. Comparison of three rodent neuropathic pain models. Exp Brain Res 1997;113:200–6.

[15] Dowdall T, Robinson I, Meert TF. Comparison of five different rat models of peripheral nerve injury. Pharmacol Biochem Behav 2005;80:93–108.

[16] Decosterd I, Woolf CJ. Spared nerve injury: an animal model of persistent peripheral neuropathic pain. Pain 2000;87:149–58.

[17] Rode F, Jensen DG, Blackburn-Munro G, Bjerrum OJ. Centrally-mediated antinociceptive actions of $GABA_A$ receptor agonists in the rat spared nerve injury model of neuropathic pain. Eur J Pharmacol 2005;516:131–8.

[18] Bourquin AF, Suveges M, Pertin M, Gilliard N, Sardy S, Davison AC, Spahn DR, Decosterd I. Assessment and analysis of mechanical allodynia-like behavior induced by spared nerve injury (SNI) in the mouse. Pain 2006; 122:14.

[19] Erichsen HK, Blackburn-Munro G. Pharmacological characterisation of the spared nerve injury model of neuropathic pain. Pain 2002;98:151–61.

[20] Kim SH, Chung JM. An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. Pain 1992;50:355–63.

[21] Gustafsson H, Sandin J. Oral pregabalin reverses cold allodynia in two distinct models of peripheral neuropathic pain. Eur J Pharmacol 2009;605:103–8.

[22] Swett JE, Torigoe Y, Elie VR, Bourassa CM, Miller PG. Sensory neurons of the rat sciatic nerve. Exp Neurol 1991;114:82–103.

[23] LaBuda CJ, Little PJ. Pharmacological evaluation of the selective spinal nerve ligation model of neuropathic pain in the rat. J Neurosci Methods 2005;144:175–81.

[24] Suzuki T, Ueta K, Tamagaki S, Mashimo T. Antiallodynic and antihyperalgesic effect of milnacipran in mice with spinal nerve ligation. Anesth Analg 2008;106:1309–15, table.

[25] Honore P, Rogers SD, Schwei MJ, Salak-Johnson JL, Luger NM, Sabino MC, Clohisy DR, Mantyh PW. Murine models of inflammatory, neuropathic and cancer pain each generates a unique set of neurochemical changes in the spinal cord and sensory neurons. Neuroscience 2000;98:585–98.

[26] Minert A, Gabay E, Dominguez C, Wiesenfeld-Hallin Z, Devor M. Spontaneous pain following spinal nerve injury in mice. Exp Neurol 2007;206:220–30.

[27] Tawfik VL, Regan MR, Haenggeli C, Lacroix-Fralish ML, Nutile-McMenemy N, Perez N, Rothstein JD, DeLeo JA. Propentofylline-induced astrocyte modulation leads to alterations in glial glutamate promoter activation following spinal nerve transection. Neuroscience 2008;152:1086–92.

[28] Sheen K, Chung JM. Signs of neuropathic pain depend on signals from injured nerve fibers in a rat model. Brain Res 1993;610:62–8.

[29] Whiteside GT, Adedoyin A, Leventhal L. Predictive validity of animal pain models? A comparison of the pharmacokinetic–pharmacodynamic relationship for pain drugs in rats and humans. Neuropharmacology 2008;54:767–75.

[30] Jarvis MF, Boyce-Rustay JM. Neuropathic pain: models and mechanisms. Curr Pharm Des 2009;15:1711–6.

[31] 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.

[32] Kontinen V, Meert T. Predictive validity of neuropathic pain models in pharmacological studies with behavioral outcome in the rat. In: Dostrovsky J, Carr D, Kolzenburg M, editors. Proceedings of the 10th world congress on pain. Seattle, WA: IASP Press; 2011. p. 489–98.

[33] Hole K, Tjolsen A. The tail-flick and formalin tests in rodents: changes in skin temperature as a confounding factor. Pain 1993;53:247–54.