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Review

Murine models of human neuropathic pain

Mariapia Colleoni, Paola Sacerdote *

Department of Pharmacology, Chemotherapy and Medical Toxicology, University of Milano, via Vanvitelli 32, 20129 Milan, Italy

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ABSTRACT

Neuropathic pain refers to pain that originates from pathology of the nervous system. Diabetes, infection (herpes zoster), nerve compression, nerve trauma, and autoimmune diseases are examples of diseases that may cause neuropathic pain. Unfortunately no satisfactory treatment is yet available for this type of pain. This consideration has led to an explosion of interest for the underlying mechanisms, accompanied by a growing number of animal models. In recent years, most of the neuropathic pain models initially developed in the rat have been translated to mice in order to exploit the resource represented by genetically modified mice. Obviously the most useful animal models of pain would be ones in which the etiology of the pain would be endogenous and not induced by the experimenters: together with the classic models based on peripheral nerve ligation, in the last years other techniques are being developed that mimic more closely clinical pain syndromes, often by attempting to induce the disease associated to neuropathic pain. Although several variables must be taken into account when using animal models for mimicking clinical neuropathic pain, the huge number of models that are now reproducible and well characterized should help to reach important goals in the comprehension of mechanisms and to discover novel therapeutic target for this disease.

1. Introduction

A definition of neuropathic pain useful for both clinical and research purposes is that recently developed by Treede et al. [1]: "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system". Neuropathic pain can be divided into peripheral or central based on the anatomic location of the lesion or the disease: peripheral nervous system (PNS, e.g. peripheral nerves, dorsal root ganglia (DRG), and dorsal roots) and central nervous system (CNS e.g. spinal cord and thalamus). These injuries arise from diabetic neuropathy, viral infections (Herpes virus, HIV), major surgeries or trauma (amputation, thoracotomy, entrapment or compression), spinal cord injury, and stroke. Examples of neuropathic pain include carpal tunnel syndrome, trigeminal neuralgia, post herpetic neuralgia, radiculopathy, phantom limb pain, complex regional pain syndromes and the various peripheral neuropathies, such as those deriving from chemotherapy. Sensory loss and spontaneous pain together with a sensory gain, such as mechanical allodynia (pain resulting from stimuli that are normally innocuous) are distinct symptoms of neuropathic pain, although this pain is also characterized by heat and mechanical hyperalgesia (increased pain responses to thermal and mechanical stimuli), all of which affect adversely the quality of patients' daily life [1,2]. Neuropathic pain is a common clinical problem affecting millions people in the USA and Europe, and it has become a major problem since unfortunately it tends to be long-lasting (neuropathic pain often lasts years or even indefinitely) and difficult to manage due to the poor efficacies and severe well-known adverse side effects associated with the current conventional antinociceptive treatments [3]. The search for new drug molecules to alleviate this intractable pain is priority nowadays, and elucidating the molecular mechanisms of neuropathic pain is an important prerequisite for the rational development of novel analgesic drugs for the therapy of this chronic pain.

Neuropathic pain arises from both PNS and CNS causes and many etiologists have been recognized in the human: a partial list is given in Table 1 [4]. Unfortunately the existence of different pathological conditions leading to the development of neuropathic pain makes more difficult the identification of a simple and reliable animal model and explains the huge numbers of models present in the literature.

2. Murine models of neuropathic pain

Animal research must always be evaluated by three general criteria: the generation of knowledge, the ability of the study to be reproduced, the relevance of the study and the predictive validity of clinical pain states. Despite the controversy on whether data from animal models can be applied to humans, this research serves as a valuable source of information in many medical areas. Animal models provide pivotal systems for preclinical studies of neuropathic pain and serve as an experimental basis for mechanistic investigations and testing new therapeutic interventions. Experiments featuring

* Corresponding author. Tel.: +39 2 50316929; fax: +39 2 50316933.
E-mail address: paola.sacerdote@unimi.it (P. Sacerdote).

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Table 1
Partial list of ethiologies of neuropathic pain in the human.

Mechanical nerve injuries/compression
Spinal cord injuries
Metabolic diseases (e.g., diabetes)
Viral diseases (e.g., herpes zoster, HIV)
Inflammatory/immunological mechanism (e.g., multiple sclerosis)
Alcoholism (vitamin B12 deficiency)
Iatrogenic: chemotherapy of cancer, AIDS or tuberculosis (e.g., cis-platinum)
Vascular lesions of the hypothalamus
Congenital (e.g., Charcot-Marie-Tooth)
Aging

behavioural measurements of neuropathic pain in animals are becoming more common over time in published papers. Non-human animals cannot self-report, but their behaviours in response to noxious stimuli can be reliably and objectively scored.

Most of animal models of neuropathic pain were generated starting from the late 1980, using rat as preferred species. More recently pain models originally developed in rats have been transposed for use in mice; a strong motive for the use of mice is the availability of genetically characterized or manipulated inbred strains, particularly transgenic mouse lines in which specific proteins or signal transduction component have been altered throughout genetic knockout technology. Although transgenic technologies has transformed basic pain research, allowing the role of individual proteins in pain to be studied even in the absence of selective ligands or antibodies, the complexity of the chronic pain phenomenon has made it difficult to asses the true value of these advances.

In addition, in pain studies more than in other animal models of disease, particular care has to be given to the strains used, since a strong influence of genetic background on pain sensitivity exists.

A common pitfall of all rodent models of neuropathic pain is the inappropriateness of the outcome measures utilized. In fact they focus on stimulus-evoked pain and hyperreflexia at a particular moment in time, whereas a high proportion of patients with neuropathic pain have ongoing, spontaneous pain and sensory loss. The recognition of spontaneous pain in experimental animals is particularly difficult. Weight loss, sleep disturbances, reduced movement, spontaneous paw lifting, scratching or shaking have all been accepted to reflect spontaneous pain [2]. Awareness is leading to the use of more complex measures of integrated pain behaviour including evaluation of neuropathic pain comorbidities, such as the presence of affective component of persistent pain [5], frequently observed in patients. However while this more comprehensive paradigm to evaluate neuropathic pain is increasingly applied to the rat model, this aspect has not been yet taken into enough consideration in the more recently developed murine models.

The numerous models of neuropathic pain in mice can be classified in many different ways.

In the present review we divide them into five gross categories:

central pain models,
peripheral nerve injury models,
models of disease-induced neuropathic pain
iatrogenic (drug-induced) neuropathic pain, and
inherited neuropathies.

3. Central pain models

These models mimic neuropathic pain resulting from CNS pathologies. Central pain syndromes represent a form of neuropathic pain that is associated with lesions of the brain or the spinal cord after a stroke or other traumatic injury. Stroke is the leading cause of disability in the industrialized world and it is estimated that up to 8% of stroke victims suffer from some form of central post-stroke pain.

3.1. Thalamic syndrome

Thalamic syndrome is a form of central pain that typically results from stroke in the thalamus and is characterized by spontaneous pain, attacks of allodynia, and dysesthesia. The lack of suitable thalamic syndrome models has hampered research into the dysregulated perception of pain resulting from stroke in the thalamus. Therefore, the development and characterization of a rodent model of thalamic syndrome was the first step to discover the underlying mechanisms of this disease and possible therapeutics. Very recently a rat model of this syndrome was developed based on a small hemorrhagic stroke lesion induced by collagenase injection in the ventral posterolateral nucleus of the rat thalamus [6]. Animals displayed hyperesthesia in response to mechanical pinch stimulation, with sensitivity localized in the hind limb and increased thermal sensitivity. This novel model has not been developed in mice yet.

3.2. Spinal cord injury (SCI)

SCI occurs in most countries at an annual rate of 20–40 persons per millions. Following mechanical injury to the spinal cord, a wave of secondary pathological changes occurs and amplifies the extent of the initial damage. Apoptosis is critical in triggering collateral damage after primary injury in SCI. Spontaneous and evoked pain are frequently sequelae of traumatic or ischemic SCI. Several models of central pathologies causing neuropathic pain were raised mainly in rats and mostly based on SCI caused by contusion or weight dropping, spinal cord compression, excitatory neurotoxins, photochemically induced ischemia, spinal cord hemisection, crushing of spinal cord. All these models were adapted for mice [7,8]. As described above, the development of reliable models of neurotrauma in mice provides great promise for evaluating overexpression or inactivation of a gene on lesion pathophysiology and functional outcome.

3.2.1. Contusive models

The spinal cord contusion is the oldest and most widely used model and has been recently employed also in mice; in addition to motor dysfunction, this injury elicits sensory dysfunction including neuropathic pain, such as tactile allodynia and thermal hyperalgesia [9-11]. Several techniques can be applied in order to mimic SCI. Some examples are dorsal column crush surgery [7]; spinal cord completely transected intervertebrally with microscissors inserted between the 9th and 10th thoracic vertebrae [12]; laminectomy at T9 or T5–T6 and compression with a vascular clip (clip compression: simple, reliable and inexpensive model) [13,14].

3.2.2. Excitotoxic models

Intraspinal or intrathecally injection of some excitoxins, such as quisqualic acid or other excitatory aminoacids (glutamate, *N*-methylaspartate, kainic acid) have been reported to produce long lasting spontaneous pain, mechanical allodynia and thermal hyperalgesia also in mice [15].

3.2.3. Photochemical model

Over the past two decades, the photochemical model of SCI, developed by Watson et al. [16] has been one of the most reliable and reproducible graded experimental models of SCI in rats [17] widely used in neurotrauma research. This model consists in an intravenous injection of the photosensitising dye, Rose Bengal, and an irradiation of the translucent dorsal surface of the T9 vertebral lamina with a 560-nm wavelength-light for 3–8 min (the beam of a xenon lamp, conveyed by fiber optics). This irradiation induced excitation of the injected dye in the spinal cord microvasculature. The resultant photochemical reaction led to vascular stasis and ischemia. The model is successfully used now also in mice where it was confirmed to