Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 7, 2014

Review Article

MODELS FOR NEUROPATHIC PAIN: A REVIEW

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Received: 29 May 2014 Revised and Accepted: 10 Jul 2014

ABSTRACT

Animal models are fundamental basis for understanding the mechanism of neuropathic pain and development of novel treatments for best possible management of the disease. Neuropathic pain models are developed for manifestation of clinical pain conditions. This review meticulously examines the technique, behavioural modifications, limitations, and advantages of most recurrently used animal models of neuropathic pain. Animal models have vastly contributed in understanding the mechanisms of this debilitating disease. Moreover, these models have also resulted in development of novel therapeutic agents and better management of the neuropathic pain. This article comprehensively reviews some of the most frequently used models of neuropathic pain.

Keywords: Allodynia, Aneurysm, Autotomy, Guarding, Hyperalgesia, Ipsilateral

INTRODUCTION

The International Association for the Study of Pain (IASP) defines neuropathic pain as "pains resulting from disease or damage of the peripheral or central nervous systems, and from dysfunction of the nervous system [1]. Neuropathic pain could be a blend of many sensory indications such as paresthesias (numbness or tingling), dysesthesias (electric shock phenomenon), hyperesthesia (increased sensitivity to mild painful stimuli), hyperalgesia (increased sensitivity to normally painful stimuli), hyperpathia (pain produced by subthreshold stimuli), spontaneous pain and allodynia (pain produced by normally non painful stimuli [2]. Pain in animals can only be judged by examining their responses to various chemical, thermal, and mechanical stimuli, with the latency or nature of response changed in the status of pain as compared to control group [3]. Animal models have been used widely in pain research as these models are capable to serve as substitute assay that can dependably evaluate the potency and efficacy of the pharmacological intervention [4]. Mechanisms causing neuropathic pain have been studied comprehensively in recent times because there has been enormous advancement in availability of clinically significant animal models to study these painful conditions. Most of the neuropathic pain models are made by causing diseases or injuries to the spinal cord or peripheral nerves. This review expresses some of the most frequently used models though many other models have also been reported [5-9]. The behavioral testing methods for acute pain can also be useful for evaluating chronic pain. The various behavioral tests include gait (limping), nocifensive signs (excessive grooming, paw licking, guarding, exploratory behavior and biting) [10-12], allodynia (Tactile allodynia and Cold allodynia) [13-15], thermal hyperalgesia (Radiant heat test and Hot-plate) [16] and mechanical hyperalgesia [17].

Central Pain Models

Neuropathic pain is an example of chronic pain with SCI [18], and at least 30 percent of patients develop reasonable central pain. Neuropathic pain results from the abnormal processing of sensory input due to injury to the CNS. Nociceptive pain related with SCI is either musculoskeletal or visceral and located in those associated structures and generally eases with rest. In animal models of central pain that depend on induced nociception after SCI, allodynia and hyperalgesia are dependent on direct observation and measurement of nocifensive behaviors, which include withdrawal of a stimulated limb or tail. However, in humans there could be difference between reported chronic pain and elicited nociception.

The commonly used models for central pain include spinal cord compression [19, 20]. Nocifensive signs crushing of spinal cord with forceps or aneurysm [21], photochemically induced injury, excitatory neurotoxin methods, and spinal hemisection [22].

Weight-drop or contusion model

This is an oldest and most widely used model for central pain. It works by causing damage to spinal cord. Dorsal surface of the spine is exposed surgically and then weight is dropped on it causing spinal cord injury (SCI). It causes complete segmental necrosis. Modifications of this model also exist and give better results [23].

Excitotoxic spinal cord injury (ESCI)

Considerable neurochemical changes take place post spinal cord injury (SCI). Intraspinal injection of neurochemicals such as serotonin, tryptamine, N methyl D aspartate and glutamate is known to produce symptoms similar to that of spinal cord injury. Many other neurochemicals have also been used to mimic SCI pain [24, 25].

Photochemical SCI model

This model makes use of photosensitizing dye erythrosin B. Erythrosin B is intravenously injected and excited by argon laser at the exposed location where it produces vessel occlusion leading to ischemia and consequently leads to parenchymal tissue damage of spinal cord. Self mutilation, hyperalgesia, mechanical and cold allodynia can be easily observed [26].

Peripheral nerve injury models

Numerous pain models have been developed that employ injury to a peripheral nerve for instance sciatic nerve which produces short-term or everlasting behavioural hypersensitivity and animal becomes susceptible to various behavioural tests such as tactile allodynia or thermal hyperalgesia. This hypersensitivity develops over several days after the peripheral nerve injury and may lead to chronic pain [27]. Allodynia is the unusual response with change in threshold level, to a non noxious stimulus, such as tactile stimulation. Hyperalgesia is a decrease in the latency of response to normally noxious stimuli, such as radiant heat [28]. Depending on the tightness of nerve ligation, the allodynia and hyperalgesia may alleviate in about 8 weeks or it may persist for several months. Partial nerve injuries include unilateral loose ligation or chronic constriction injury (CCI) of the sciatic nerve. Due to this the animal may persistently hold the ipsilateral hind paw in a guarded position [29].

Chronic constriction injury model (CCI or Bennett model)

In this model sciatic nerve of right or left side is loosely ligated at four places at the mid thigh level. Rats with CCI display excessive licking, limping of ipsilateral hind paw, guarding, self-mutilation and

attack denervated area. Hyperalgesia due to noxious thermal and mechanical stimuli is detectable, alongwith cold allodynia and tactile allodynia. All pain symptoms persist approximately for two months [29].

Partial sciatic nerve ligation model (PSL or Seltzer model)

This model rat model for inducing neuropathic pain was suggested by Seltzer and co- workers in 1990. The technique requires ligation of the ipsilateral sciatic nerve at upper thigh level, so that 1/3–1/2 width of the sciatic nerve is trapped in ligature. After PSL rats display allodynia, guarding, licking, spontaneous pain, hyperalgesia to both thermal and mechanical within few hours of ligation. All the signs and symptoms last for over seven months [30].

L5 /L6 spinal nerve ligation model (SNL)

In the SNL, L5 and L6 spinal nerves are unilaterally and tightly ligated at a location distal to the dorsal root ganglia. Hyperalgesia and allodynia develop soon after ligation. The symptoms last approximately for four months. Behavioural signs such as licking, lifting of ipsilateral hind paw, guarding are present. Autotomy is not present in this model [31].

Sciatic cryoneurolysis model (SCN)

This model implies freezing of sciatic nerve. Touch allodynia and autotomy are present after SCN. Cryoneurolysis-induced nerve injury is sometimes reversible in nature so healing process od disease can be studied in this model. Touch allodynia, autotomy and spontaneous nociceptive behaviours last for shorter duration (15-21 days) as compared to above mentioned models [32, 33].

L5 spinal nerve ligation

This model has not been completely characterised yet. It is easier to execute than L5/L6 ligation and rats show prolonged signs of hyperalgesia and mechanical allodynia. It is a better model for studies involving mice. Chung model may mean L5/L6 spinal nerve ligation or only L5 ligation [34].

Axotomy model (complete sciatic nerve transection; neuroma model)

This is one of the oldest models for inducing neuropathic pain. It employs transection of entire sciatic nerve at mid-thigh level [35]. The exposed sciatic nerve is freed from the connective tissue and then it is tightly ligated by nylon suture, proximal to the junction of tibial and peroneal divisions at two locations with about 1-cm gap. The nerve is then completely transected among the pair of ligatures, and 5 mm of the nerve between the ligatures is removed to check the re-joining of nerves due to regeneration. Following complete nerve transection, a neuroma develops at the proximal nerve end consisting of regenerative nerves emerging in all directions [36].

Caudal trunk resection

In this model the left inferior caudal trunk is resected between the S3 and S4 spinal nerves due to which there is development of mechanical, cold, and warm allodynia in the tail which persists for several weeks. The symptoms of mechanical and thermal allodynia appear in a day after the nerve injury [37].

Spared nerve injury (SNI)

This is a latest animal model of neuropathic pain developed by Decosterd and Woolf [38]. In this model, rats are anesthetized. The skin on the lateral surface of the left thigh is shaved and a dissection is made straight through the biceps femoris muscle. The sciatic nerve and its three terminal branches namely sural, common peroneal, and tibial are exposed. After that, the tibial and the common peroneal nerves are tightly ligated followed by axotomy of 2 mm of distal nerve. An enormous care is taken to avoid any contact with the sural nerve. Since sural nerve remains totally untouched so this model is referred as 'Spared Nerve Injury (SNI) model'. Two other modifications of SNI injury of the sciatic nerve have also been developed by similar surgical procedure, but by using different combinations of nerve transections. The mechanical and thermal hyperalgesia and allodynia occur within four days of SNI, which continues for several months post injury [38, 39].

Neuropathic pain due to medical conditions

In human beings certain ailments such as diabetes, shingles and cancer are responsible for causing neuropathic affliction. Diabetes mellitus is the leading cause of neuropathy in the Western world [40]. In one series of studies, neuropathy is present in 66% of diabetic patients [34]. Shingles is associated with painful rashes. Shingles is also associated with painful postherpatic neuralgia which may persist throughout life. [41]

Diabetic neuropathic pain model (DNP)

Neuropathy occurs for both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), suggesting that hyperglycaemia is the primary etiologic factor [42] A few diabetic models are available, e.g. insulin deficient BB rats [43] and NOD (non obese diabetic mice). [44] Most frequently used chemical methods to induce diabetic neuropathic pain are by streptozotocin. The behavioural signs observed in STZ-treated animals are allodynia and thermal sensitivity probably due to the sensitization of cutaneous nociceptors associated with Aδ and C fibers [45, 46].

Postherpetic neuralgia model (PHN)

Varicella zoster virus (VZV) is an extremely virulent neurotropic virus and it is responsible for causing varicella (chickenpox) as the primary infection and at advance stage the virus transports retrospectively down the axons of sensory neurons from the skin to set up a latent infection within sensory ganglia of the peripheral nervous system [47]. Postherpatic neuralgia (PHN) is characterized by the presence of both spontaneous and evoked pain symptoms. A recent study concluded persistent allodynia and hyperalgesia in a rat model of latent varicella zoster infection [48].

Drug induced neuropathic pain

Vincristine induced neuropathic pain

The alkaloid vincristine is an antineoplastic drug which causes neuropathy. Vincristine has been used widely as chemotherapeutic agents for the treatment of several malignancies including breast cancer, leukaemia, lymphomas, and primary brain tumours [49]. However, clinical use of vincristine has been associated with the development of neurotoxicity of peripheral nerve fibres. Painful paresthesia is generally the very first sign in most of the patients. Vincristine is known to cause dose dependent neuropathy [50].

Cisplatin induced neuropathic pain

Cisplatin has established its efficacy against many different types of malignancies such as ovarian, head, neck, testicular, colon and lung cancers. Emesis, anorexia, nephrotoxicity, myelo-suppression, ototoxicity and peripheral neuropathy is frequently coupled with its use [51].

Paclitaxel-induced neuropathy

Paclitaxel derived from Taxus brevifolia. It is potent anti-cancer drug and is usually incorporated in chemotherapy for the treatment of breast, ovarian, head and neck cancers. Paclitaxel is known to cause sensory neuropathies which are generally categorized by tingling, numbness, mechanical allodynia, cold allodynia, and spontaneously evoked burning pain in distal extremities [51, 52].

Docetaxel-induced peripheral neuropathy

It is a semisynthetic taxane, which is broadly used to treat various malignancies such as breast, ovarian and non-small cell lung cancers [53]. Its efficiency is restricted due to throbbing pain in peripheral neuropathies. It produces neuropathy in dose dependent manner [54]. In Docetaxel-induced neuropathic pain model i.v. injection of docetaxel (5; 10 or 12.5 mg/kg) for 4 weeks is given to induce neuropathy in rats. Docetaxel-treated rats demonstrate decreased tail nerve conduction velocity, changes in thermal threshold, and degeneration of foot pad skin nerves [55, 56].

Anti-HIV drugs-induced neuropathy

Highly active anti-retroviral therapy (HAART) is the most efficient therapy for AIDS and encompasses various nucleoside reverse

transcriptase inhibitors (NRTIs) such as zalcitabine, didanosine and stavudine as its components. These drugs have a prominent side effect to produce painful neuropathies and to enhance pain perception caused by HIV-1 infection. [57,58] Some NRTIs are more prominent to cause neuropathy than others such as zalcitabine which is more potent than didanosine, which is further more potent than stavudine especially for causing sensory neurotoxicity. The other NRTIs namely zidovudine and abacavir are not known to cause any neuropathy [57]. Anderson et al. [59] established the neurotoxic effect of zalcitabine in rabbits, and Schmued et al. illustrated the effect of didanosine in brain and nerves of rats [60].

CONCLUSION

Neuropathic pain has varied etiology which is difficult to understand. The development of animal models has significantly enhanced our understanding about pain and various mechanisms contributing to it. Peripheral nerve injury models such as PSL, SCL,CCI and neuroma models are more frequently used for mimicking peripheral pain whereas; spinal cord injury models are a superior alternative for understanding of mechanisms leading to central pain. Though rat models can also be employed in mice but different species elicit different response to similar injury or disease. Additionally pain models due to chemotherapeutic agents, diabetes, HIV have contributed to better understanding of their pathophysiology and management.

CONFLICT OF INTERESTS

Declared None

ACKNOWLEDGEMENT

I express immense gratitude to I.T.S Paramedical College for granting me with all the amenities essential in development of this review article.

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