Simulations of Neuropathic Pain

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ABSTRACT - *Animal models are necessary basis for considerate the mechanism of neuropathic pain and expansion of novel treatments for best possible organization of the disease. Neuropathic pain models are developed for manifestation of clinical pain conditions. This review methodically examines the technique, behavioral modifications, limitations, and compensations of most recurrently used animal models of neuropathic pain. Animal models have vastly subsidized in understanding the mechanisms of this devastating disease. Additionally, these models have also resulted in development of novel therapeutic agents and better management of the neuropathic pain. This article expansively reviews some of the most frequently used models of neuropathic pain.*

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

I. INTRODUCTION

The International Association for the Study of Pain (IASP) describes neuropathic pain as "pains resulting from disease or damage of the peripheral or central nervous systems, and from dysfunction of the nervous system. Neuropathic pain could be a intermingling of many sensory indications such as paresthesia's (numbness or tingling), dysesthesias (electric shock phenomenon), hyperesthesia (increased understanding to mild painful stimuli), hyperalgesia (inflamed sensitivity to normally painful stimuli), hyperpathia (pain formed by subthreshold stimuli), spontaneous pain and allodynia (pain twisted by normally non painful stimuli. Pain in animals can only be mediated by examining their responses to various chemical, thermal, and mechanical stimuli, with the potential or nature of response changed in the status of pain as associated to control group. Animal models have been used widely in pain exploration as these models are talented to serve as auxiliary assay that can regularly evaluate the potency and adeptness of the pharmacological intervention. Mechanisms causing neuropathic pain have been premeditated comprehensively in recent times because there has been enormous development 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 bordering nerves. This review expresses some of the most regularly used models though many other models have also been recounted. The behavioral testing methods for acute pain can also be useful for appraising chronic pain. The various behavioral tests include gait (limping), nocifensive signs (excessive grooming, paw licking, defending, exploratory behavior and biting), allodynia (Tactile allodynia and Cold allodynia), thermal hyperalgesia (Radiant heat test and Hot-plate) and mechanical hyperalgesia.

II. CENTRAL PAIN MODELS

Neuropathic pain is an example of chronic pain with SCI, and at least 30 percent of patient'sprogresssensible central pain. Neuropathic pain results from the irregular processing of sensory input due to injury to the CNS. Nociceptive pain associated with SCI is either musculoskeletal or visceral and located in those associated assemblies and generally eases with rest. In animal models of central pain that be contingent on induced nociception after SCI, allodynia and hyperalgesia are reliant on direct observation and measurement of nocifensive behaviors, which include withdrawal of aenthused limb or tail. Though, in humans there could be modification between reported chronic pain and elicited nociception.

The frequently used models for central pain embrace spinal cord compression. Nocifensive signs crushing of spinal cord with tongs or aneurysm, photo chemically induced injury, excitatory neurotoxin methods, and spinal hemi section.

2.1 Weight-drop or contusion model:

This is an eldest and most widely used model for central pain. It works by producing damage to spinal cord. Dorsal surface of the spine is unprotected surgically and then weight is released on it causing spinal cord injury (SCI). It causes comprehensive segmental necrosis. Modifications of this model also exist and give better results.

2.2 Excitotoxic spinal cord injury (ESCI):

Significant 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 harvest symptoms similar to that of spinal cord injury. Several other neurochemicals have also been used to mimic SCI pain.

2.3 Photochemical SCI model:

This model makes use of photosensitizing dye erythrosine B. Erythrosine B is intravenously inoculated and excited by argon laser at the visible location where it produces vessel obstruction leading to ischemia and consequently leads to parenchymal tissue damage of spinal cord. Self-mutilation, hyperalgesia, mechanical and cold allodynia can be easily observed.

2.4 Peripheral nerve injury models:

Numerous pain representations have been established that employ injury to a peripheral nerve for occurrence sciatic nerve which produces short-term or everlasting behavioralsensitivity and animal becomes susceptible to various communication tests such as tactile allodynia or current hyperalgesia. This hypersensitivity develops over several days after the bordering nerve injury and may lead to chronic pain. Allodynia is the unusual response with change in threshold level, to a non-noxious stimulus, such as tactile motivation. Hyperalgesia is a diminution in the latency of reply to normally noxious stimuli, such as radiant heat. Contingent 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 determinedly hold the ipsilateral hind paw in a defended position.

2.5 Bennett model:

In this model sciatic nerve of right or left side is roughly ligated at four places at the mid-thigh level. Rats with CCI presentation excessive licking, limping of ipsilateral hind paw, defending, self-mutilation andattack denervated area. Hyperalgesia due to noxious thermal and motorized stimuli is detectable, along with cold allodynia and tactile allodynia. All pain indications persist approximately for two months.

2.6 Seltzer model:

This model rat model for tempting neuropathic pain was recommended 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 and hyperalgesia to both thermal and mechanical within few periods of ligation. All the signs and symptoms last for over seven months.

III. DRUG INDUCED NEUROPATHIC PAIN

3.1 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 numerous malignancies comprising breast cancer, leukemia, lymphomas, and primary brain tumours. Though, clinical use of vincristine has been associated with the expansion 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.

3.2 Cisplatin induced neuropathic pain:

Cisplatin has reputable its effectiveness against many diverse types of malignancies such as ovarian, head, neck, testicular, colon and lung cancers. Emesis, anorexia, nephrotoxicity, myelo-suppression, ototoxicity and peripheral neuropathy is frequently joined with its use.

3.3 Paclitaxel-induced neuropathy:

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

3.4 Docetaxel-induced peripheral neuropathy:

It is a semisynthetic taxane, which is broadly used to treat several malignancies such as breast, ovarian and non-small cell lung cancers. Its efficacy is restricted due to throbbing pain in peripheral neuropathies. It harvests neuropathy in dose reliant on manner. 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 deterioration of foot pad skin nerves.

3.5 Anti-HIV drugs-induced neuropathy:

Highly active anti-retroviral therapy (HAART) is the most effective therapy for AIDS and encompasses various nucleoside reversetranscriptase inhibitors (NRTIs) such as zalcitabine, didanosine and stavudine as its components. These drugs have a protruding side consequence to produce painful neuropathies and to enhance pain awareness caused by HIV-1 infection.Some NRTIs are more prominent to cause neuropathy than others such as zalcitabine which is more powerful than didanosine, which is more potent than stavudine particularly for causing sensory neurotoxicity. The other NRTIs namely zidovudine and abacavir are not known to cause any neuropathy. Anderson et al. recognized the neurotoxic effect of zalcitabine in rabbits, and Schmued et al. illustrated the consequence of didanosine in brain and nerves of rats.

IV. CONCLUSION

Neuropathic pain has different etiology which is problematic to understand. The development of animal models has knowingly enhanced our considerate about pain and various mechanisms contributing to it. Peripheral nerve injury models such as PSL, SCL,CCI and neuroma models are more commonly used for mimicking peripheral pain whereas; spinal cord injury models are a superior substitute for considerate of mechanisms leading to central pain. Though rat models can also be employed in mice but diverse species elicit altered response to similar injury or

disease. Furthermore pain models due to chemotherapeutic agents, diabetes, HIV have contributed to better understanding of their pathophysiology and management.

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