An update on neuropathic pain models

Seema Thakur, Neha Srivastava

Assistant Professor, Faculty of Pharmaceutical Sciences, PCTE Group of Institutes, Near Baddowal Cantt, Ferozepur Road, Ludhiana, 142021, Punjab, 142021

Email: thakurseema1983@yahoo.co.in

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Abstract

An animal model of pain offers a powerful tool in order to understand the mechanism involved in peripheral nerve injury for preclinical study of pain. A battery of neuropathic pain models has been developed to simulate the clinical pain conditions with diverse etiology. 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. For reasons of reproducibility and simplicity, most studies of neuropathic pain are based upon animal models of traumatic nerve injury, usually in the rat sciatic nerve. The present review exhaustively discusses the methodology, behavioral alterations of different animal models of neuropathic pain along with their modifications. Development of these models has contributed immensely in understanding the chronic pain and underlying peripheral as well as central pathogenic mechanisms.

Keywords:
Peripheral neuropathy, Neuropathic pain, Chronic constriction injury, Spinal nerve ligation, Partial sciatic nerve ligation

Introduction

Pain is an unpleasant sensory and emotional experience often associated with actual or potential tissue damage, or described in terms of such damage [1]. Pain can be of two types: acute pain and chronic pain as shown in fig. 1. Acute pain is the pain results from disease, inflammation, or injury to tissues whereas chronic pain is widely believed to represent disease itself that can be made much worse by environmental and psychological factors. Chronic pain persists over a longer period of time than acute pain and is resistant to most medical treatments. Chronic pain can be nociceptive or neuropathic.

Nociceptive pain is protective and is a normal response to tissue injury in comparison to that neuropathic pain is a pathologic or maladaptive pain, results from damage to the nervous system, producing pain in the absence of stimulation of nociceptors or inappropriate response to stimulation of nociceptors [1] often characterized by Hyperalgesia (An increased response to a stimulus which is normally painful) and Allodynia (Pain due to stimulus which does not normally provoke pain).

The normal pathways involved in the transmission of pain begin with stimulation of nociceptors including those that respond to chemical irritant stimuli such as the vanilloid receptor VR1, ATP purinoceptor P2X3 and noxious heat stimuli such as VR1 and VR1L. Signals resulting from intense mechanical and thermal stimulate A-delta fiber nociceptor and intense mechanical, thermal and chemical stimuli stimulate polymodal C-nociceptor.

Affenter fibers synapse in Rexed’s lamina I, II and V in the spinal cord, which is the first level of modulation. Opiate receptors and interneurons are present at the dorsal horn. There are also descending inputs from the hypothalamus, periaqueductal gray. Opioids, nor-epinephrine (NE) and serotonin (5-HT3) have modulatory effects on...
pain transmission. Animal models are being developed to better understand the disease pathogenesis and develop drugs for neuropathy. In the present review, we have discussed various animal models, which may open vistas for developing new drugs to treat nephropathy. This led to attempts for developing different nerve injury models in animals as surrogates for neuropathic pain (Table 1).

### Table 1: List of different animal models of neuropathic pain

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### Animal models of neuropathic pain

#### Peripheral nerve injury models

**Chronic constriction injury (CCI) model**

CCI is the most commonly used and highly validated model. Bennett and Xie reported a rat model unilateral mononeuropathy in 1988. Briefly, the rats are anesthetized with pentobarbital (40 mg/kg) sodium. The common sciatic nerve is exposed at the level of the middle of the thigh by blunt dissection through biceps femoris. Proximal to the sciatic’s trifurcation, about 7 mm of nerve was freed by blunt dissection through the biceps femoris. After surgery, all animals were administered gentamicin (5 mg/kg) to prevent sepsis. Neuropathic pain symptoms such as hyperalgesia and allodynia developed from day 3 after surgery and persisted for 7 mo [3, 4].

**Partial sciatic nerve ligation (PSNL) model**

Seltzer et al. reported a rat model of partial sciatic nerve ligation in 1990. In this model, the right sciatic nerve is exposed at the high-thigh level and ligated so that 1/3-1/2 thickness of the sciatic nerve is trapped in the ligature [5]. Symptoms of neuropathic pain i.e. hyperalgesia and allodynia develop immediately after injury i.e. 1 hr after injury and symptom develops for at least 7 mo [6, 7] as well as these symptoms seen in human causalgia patients. In this method, the animal also shows mirror image pain in which pathological nociception occurs on the side contralateral to the injured side. The sensitivity of this method is 61% [8].

**LS/L6 spinal nerve ligation (SNL) model**

Kim and Chung reported another unilateral mono neuropathic rat model in 1992. In this model, the unilateral ligation of two spinal nerves (LS and L6) is performed under thiopental sodium anesthesia (50 mg/kg). Briefly, the left paraspinal muscles are separated from the spinous process at the L4-S2 levels. The L6 transverse process is removed to identify the L4-L6 spinal nerves visually. The left L5 and L6 spinal nerves is isolated and tightly ligated with 6-0 silk thread. After that the wound is sutured [9-11]. Symptoms developed immediately after injury and maintained for at least 4 mo [12] as well as symptoms seen in human causalgia patients. Animals also show mirror-image pain similar to those of Seltzer model. All three models i.e CCI, PSNL and SNL can be produced in mice, and a direct comparison of these three models has been reported [13]. Authors demonstrated a similar onset of sensory threshold changes in mechanical and cold allodynia in all three models, but a greater magnitude of change in sensory threshold in SNL. All three models demonstrated significant cold and mechanical allodynia at 3 d after injury and spontaneous pain at one day after the injury. Mechanical allodynia was determined by the application of an 8.4 mN Von-Frey hair. The allodynia was greatest in SNL model with a ~ 80% response frequencies, followed by PNL (~60% response frequency) and CCI (~45% response frequency). They also demonstrate a more significant involvement of the sympathetic nervous system component in sensory response to SNL than following PNL or CCI. The sensitivity of this method was 68% [8].

**LS spinal nerve ligation**

Kim and Chung also reported the single L5 nerve ligation. In this method, left L5 spinal nerve is tightly ligated 5 mm distal to the dorsal root ganglia with 4-0 Mersilk [9]. This method is much easier to perform than L5/L6 ligation. This method is also performed in mice.

**Spare nerve injury (SNI) model**

Decosterd and Woolf reported the rat model of spared nerve injury in 2000. Briefly, the rat is anaesthetized with chloral hydrate (80 mg/kg i.p) and skin of the left lateral thigh was incised. The cranial and the caudal parts of biceps femoris muscles are separated and held apart by retractor to expose the sciatic nerve and its three branches: the sural, common peroneal and tibial nerves. The tibial
and common peroneal nerves are tightly ligated with 4/0 silk and 2-3 mm of the nerve distal to the ligation was removed. Any stretching or contact with the intact sural nerve is avoided. Then the skin and muscle is sutured [14, 15]. This method produces robust changes in behavioral symptoms i.e. allodynia and hyperalgesia [6, 7]. Symptoms of neuropathic pain developed immediately after surgery and maintained for at least 7 mo [16].

Tibial nerve injury (TNI) model
The tibial nerve injury model is a novel, surgically uncomplicated, rat model of neuropathic pain based on a unilateral transaction (neurotomy) of the tibial branch of the sciatic nerve. Tibial nerve injury was performed under pentobarbital anesthesia. Distal to the trifurcation of the left sciatic nerve, the tibial branch of the sciatic nerve is ligated, whereas the sural and common peroneal nerves remained uninjured [17]. Behavioral symptoms develop within 2 w after surgery and persist for at least 9 w.

Spinal nerve transection (SNT)
In this model, unilateral mononeuropathy is produced according to the method of described earlier by Colburn et al. [18]. Briefly, rats are anesthetized with halothane in an oxygen carrier (induction 4 %, maintenance 2 %). A small incision to the skin overlying L5-S1 is made followed by retraction of the paravertebral musculature from the vertebral transverse processes. The L5 transverse process is partially removed exposing the L4 and L5 spinal nerves. Then the L5 spinal nerve is identified, lifted slightly, and transected [19]. The wound is irrigated with saline and closed in two layers with 3-0 polyester suture and surgical skin staples.

Sciatic cryoneurolysis model (SCN)
SCN was performed as described by De Leo et al. [21, 22]. Briefly, a segment (~1.0 cm) of the common sciatic nerve proximal to its primary trifurcation is exposed by blunt dissection and suspended across forceps in the surgical opening. The nerve is lesioned in a 30-s freeze, 5-s thaw, and 30-s freeze cycle using a 2-mm diameter cryoprobe cooled to -60 °C with nitrous oxide as the refrigerant. The resulting pellet from each 75 cm² flask was resuspended in 150 µm aqueous saline and harvested when cells exhibited approximately 80% cytopathic effect (cpe) on microscopy (equivalent to 104 to 105 plaque forming units, pfu). Cpe refers to the destruction of normal fibroblast cell architecture due to viral lytic infection and is characterized by the presence of vacuoles and granules. Virus-infected cells are gently scraped from the flask surface onto which they had formed a monolayer culture, and the cell suspension is centrifuged at 1500 r.p.m. 4 °C for 15 min. The resulting pellet from each 75 cm² flask was resuspended in 105 µl sterile phosphate buffer solution. Animal are then anesthetized with pentobarbitone, 40 mg/kg i.p. and then s.c. injected with 50 µl viral inoculum into the mid-plantar glabrous footpad of the left (ipsilateral) hind limb using a 25 gauge needle. Control animals received a similar injection of uninected fibroblast cells (mean count 6–8x106 cells/75 cm² flasks). Virus-induced neuropathic pain symptom i.e mechanical allodynia develops on day 4 and remains for 6 w [31]. This model will prove useful in elucidating the pathophysiology of zoster-associated pain and provide a tool for pre-clinical screening of analgesic drugs [31].

Sciatic inflammatory neuritis (SIN) model
Apart from trauma of peripheral nerve, most of the neuropathies developed by inflammation or infection. Gacur et al reported a new model of sciatic inflammatory neuritis in 2001. In this method, firstly the peri-sciatic catheter is implanted then after the injection of zymosan (40, 80 and 160 µg) is given bilaterally around sciatic nerve [23]. Allodynia was observed 2-4 h after injury [21, 22]. One potential advantage of this method is that cryoneurolysis-induced nerve injury may be reversible, thus providing an opportunity to study the effect of transient nerve injury and the healing process. Behavioral symptoms such as touch-evoked allodynia last for about 15-21 d as compared to other peripheral injury models such as CCI, SNL and PSNL.

Sciatic nerve cuffing
Benbouzid [24] reported the model of sciatic nerve cuffing, a model of sustained neuropathic pain in mice in 2007. Briefly, in this method surgery is done under aseptic conditions and ketamine/xylazine anesthesia (ketamine: 17 mg/ml i.p, xylazine: 2.5 mg/ml i.p, 4 ml/kg). The common branch of the right sciatic nerve is exposed and a 2 mm long split section of polyethylene tubing (ID = 0.38 mm, ED = 1.09 mm; PE-20) is placed around it (Cuff group). The shaved skin layer is closed using suture. Thermal hyperalgesia and allodynia develop on day 1 and heat hyperalgesia persists for 2 w but mechanical allodynia persists for 2 mo. Sciatic nerve cuffing in mice is a pertinent model for the study of nociceptive and emotional consequences of sustained neuropathic pain.

Disease related peripheral neuropathy
In humans, shingles and diabetes are a very common disease with neuropathic symptoms (25). Shingles is characterised by a very painful rash. Some patient suffers from postherpetic neuralgia following acute shingles, which can persist for many years and even for life. Diabetes is associated with increased risk of a number of well-known microvascular complications (eg, retinopathy, nephropathy, and neuropathy) and macrovascular complications (eg, stroke, coronary heart disease, peripheral vascular disease) [26]. Diabetic peripheral neuropathy (DPN) is probably the most common of the microvascular complications, affecting approximately 50% of persons with diabetes. Although hyperglycemia causes neuropathy are not fully understood. Recent evidence suggests that hyperglycemia contributes to a state of heightened oxidative stress and the generation of reactive oxygen species that are important in the development of neuropathy and other microvascular diabetes complications [25, 26]. Several metabolic pathways probably contribute to hyperglycemia-induced oxidative stress, including the polyol pathway, protein kinase C (PKC) activation, and accumulation of the end products of auto glycation (ie, advanced glycation end products).

Postherpetic neuralgia model (PHN)
Postherpetic neuralgia [27] is characterized by the presence of both spontaneous and evoked pain symptoms such as burning and aching and often superimposed by allodynia. In a rodent model of varicella zoster virus [28-30], VZV is propagated on fibroblast (primary human embryonic lung) cells and harvested when cells exhibited approximately 80% cytopathic effect (cpe) on microscopy (equivalent to 104 to 105 plaque forming units, pfu). Cpe refers to the destruction of normal fibroblast cell architecture due to viral lytic infection and is characterized by the presence of vacuoles and granules. Virus-infected cells are gently scraped from the flask surface onto which they had formed a monolayer culture, and the cell suspension is centrifuged at 1500 r.p.m. 4 °C for 15 min. The resulting pellet from each 75 cm² flask was resuspended in 150 µl sterile phosphate buffer solution. Animal are then anesthetized with pentobarbitone, 40 mg/kg i.p and then s.c. injected with 50 µl viral inoculums into the mid-plantar glabrous footpad of the left (ipsilateral) hind limb using a 25 gauge needle. Control animals received a similar injection of uninected fibroblast cells (mean count 6–8x106 cells/75 cm² flasks). Virus-induced neuropathic pain symptom i.e mechanical allodynia develops on day 4 and remains for 6 w [31]. This model will prove useful in elucidating the pathophysiology of zoster-associated pain and provide a tool for pre-clinical screening of analgesic drugs [31].

Diabetic neuropathy pain model
The most commonly and widely used chemically-induced model of diabetic neuropathy is streptozotocin-induced diabetic neuropathy. Streptozotocin is a chemotherapeutic agent and it kills insulin-secreting islet cells. Briefly, diabetes is induced in rats by single injection of STZ (45-75 mg/kg, i.p.) dissolved in citrate buffer (pH 4.5-5.5) [25, 31]. Diabetes is observed 48-72 hr after the injection of STZ by measurement of glycated (ie, advanced glycation end products). Diabetes is characterized by hyperglycemia, allodynia, along with motor deficits and reduced axonal and nerve conduction velocity.

Cancer pain models
Cancer-related pain may be caused by tumor infiltration or compression of nerve, plexus, or roots, immune-reactive and pronociceptive substances released from rumors, or by treatment (chemotherapy, radiation, or surgery).

Chemotherapy-induced peripheral neuropathy models
Major and severe side effects of chemotherapy are peripheral neuropathy and bone marrow suppression. Various classes of
chemotherapeutic agent particularly the vinca alkaloids, platinum compounds and taxol are responsible for causing toxicity particularly the neurotoxicity and also inducing neuropathy. When these chemicals are administered to an animal, they produce neuropathy which may be used to study causes, prevention and treatment of their neurotoxicity.

**Vincristine-induced peripheral neuropathy model (VIPN)**

Vincristine, a vinca alkaloid, is mainly used to treat cancer particularly acute leukemia, Kaposi sarcoma, Hodgkin disease and other lymphoma. It acts by binding to tubulin protein and inhibits microtubule polymerization, thus causing the mitotic arrest. Severe neuropathies result from vincristine administration, so it is a limiting factor for dose escalation which is often needed to achieve the desired anti-cancer activity. Several methods have been described to induce neuropathic pain by vincristine [35-37]. Daily injection of vincristine (single doses of 50, 100 and 200 μg/kg) for 10 d (5 consecutive drug days+2 drug-free days+5 more drug days) in rat produces the symptoms of hyperalgesia and allodynia. Continuous intravenous vincristine infusion can also produce allodynia, but does not show the symptoms of hyperalgesia [35-38]. The reason for this remains to be clarified.

**Paclitaxel-induced peripheral neuropathy model (TIPN)**

Paclitaxel is a chemotherapeutic agent obtained from the Pacific yew tree Taxus brevifolia and is used to treat ovarian and breast cancer, and non-small cell lung cancer. It acts by binding to tubulin (at a site different from vinca alkaloid) and blocks the polymerization of microtubules. It produces the dose-dependent neuropathy and incidence is 50-90%. Several rat or mouse model of paclitaxel-induced neuropathic pain model have been reported. Briefly, Paclitaxel (2 mg/kg, i.p.) was administered on four alternative days (days 0, 2, 4 and 6) to rats and it produces the symptoms of thermal hyperalgesia and allodynia [39-43].

**Cisplatin-induced peripheral neuropathy (CIPN)**

Cisplatin (CDDP) and the other platinum-derived drugs are among the most effective antineoplastic agents, but they are severely neurotoxic. The clinical features of CDDP neurotoxicity in humans are mainly ataxia, pain, and sensory impairment secondary to accumulation of CDDP in the dorsal root ganglia (DRG) and subsequent damage, resulting in secondary nerve fiber axonopathy. Severe neuropathy can occur in 3% to 7% of treated cases with single agents but can increase to 38% with combined regimens. Peripheral neuropathy induced by injection of cisplatin at a dose of 2 mg/kg i.p. twice weekly for 8 times using a volume of 4 mL/kg [44, 45].

**Oxaliplatin-induced peripheral neuropathy (OIPN)**

Oxaliplatin is a third-generation platinum-based chemotherapeutic agent used to treat advanced metastatic colorectal cancer, ovarian and breast cancer, and lung cancer. It is structurally similar to cisplatin but contains a 1, 2-diaminocyclohexane carrier ligand. This modification enhances the antitumor activity. Since it is a platinum derivative, oxaliplatin induces neurotoxicity but not the nephrotoxicity, as with cisplatin. Several models have been reported in rat as well as in mice. Briefly, oxaliplatin induces neuropathy by i.v injection at one of the three different doses, 1, 2, 4 mg/kg, twice weekly for four-and-a-half consecutive weeks [46, 47]. It shows the both hyperalgesia and allodynia [6, 7].

**Bone cancer pain models**

Bone cancer pain is one of the most common cancer-related pains. Bone cancer can be primary or metastatic from the breast, prostate, ovary and lung tumors. Deep pain with a burning and stabbing sensation is often described by bone cancer patients.

**Rat tibial bone cancer model (TBC)**

In this model, MRTT-1 rat mammary gland carcinoma cells are injected into the tibial bone of rats [48]. MRTT-1 rat mammary gland carcinoma cells are prepared by culturing the cells in the medium containing RPMI 1640, 10 % l-glutamine and 2 % penicillin/streptomycin. Cells are then released from the plastic by brief exposure to 0.1 % w/v trypsin and then prepared for injection. Ten millimeters of the medium is centrifuged for 3 min at 1200 rpm, and the resulting pellet is washed twice with 10 ml of Hank’s balanced salt solution without Ca²⁺, Mg²⁺ or phenol red and then centrifuged for 3 min at 1200 rpm. The final pellet is then suspended in 1 ml of Hank’s solution and cells are counted by using a hemocytometer. Cells are then diluted to achieve final concentrations for injection and keep in ice until injection. Destruction of bone can be identified within 10 d of tumor cell injection. Behavioral symptoms include hyperalgesia and allodynia develops 10-12 d after tumor cell injection. Bisphosphonate as Zoledronic acid and cyclooxygenase (COX)-2 are effective in attenuating the mechanical hyperalgesia and allodynia on chronic treatment [49].

**Mouse femur bone cancer pain model (FBC)**

In this model, osteolytic mouse sarcoma NCTC2472 cells are used to produce bone cancer by injecting tumor cells into the marrow space of the femur bone and then sealing the injection site [50]. Bone destruction and osteoclastogenesis occurs 5 d after the injection. Spontaneous pain symptoms such as flinching, nocifensive behavior as well as changes in the neurochemical marker develops within 14 d. Drugs like opioids and COX-2 inhibitors are effective in reversing these symptoms. But the effect of COX-2 inhibitors in this model is different from TBC model suggests that different bone cancer models have different pathophysiology which is based upon animal species, tumor type, and location.

**Mouse calcoskeletal bone cancer pain model (CBC)**

This model is similar to FBC model, except that NCTC2472 cells are injected into mouse calcoskeletal bone [50]. Symptoms such as osteolysis, spontaneous pain i.e. paw licking and evoked pain i.e mechanical and cold allodynia occurs 6 d after implantation and remains for at least 16 d [50, 51].

**HIV-induced neuropathy models**

Distal symmetrical polyneuropathy (DSP) affects 15–50% of people living with HIV [52], 50–60% of whom have measurable sensory abnormalities and on-going, paroxysmal or stimulus-evoked pain associated with HIV infection and is characterized by length-dependent axonal degeneration of sensory fibers [53, 54]. There are two predominant (and clinically similar) settings in which painful HIV-DSP may occur. First, a disease-related DSP associated with HIV-infection per se; or secondly a drug-induced DSP associated with the use of nucleoside reverse transcriptase inhibitors (NRTI), particularly the didoxoynucleosides; zidovudine (ddd), didanosine (ddI) and stavudine (d4T), as part of highly active anti-retroviral therapy (HAART) [53, 54]. The neuropathy in these rodents is characterized by distal degeneration of unmyelinated sensory axons, similar to the “dying back” pattern of C-fiber loss seen in patients with HIV-SN. This model will be useful in examining mechanisms of distal axonal degeneration and testing potential neuroprotective compounds that may prevent the development of the sensory neuropathy [55, 56].

**HIV gp-120 associated sensory neuropathy**

A distal symmetrical sensory peripheral neuropathy is frequently observed in people living with Human Immunodeficiency Virus Type 1 (HIV-1). This neuropathy can be associated with viral infection alone, probably involving a role for the envelope glycoprotein gp120; or a drug-induced toxic neuropathy associated with the use of nucleoside analogue reverse transcriptase inhibitors as a component of highly active anti-retroviral therapy. In this method, briefly, under 1–2% isoflurane anaesthesia in O₂ and N₂0, and aseptic surgical conditions, the left sciatic nerve is exposed in the popliteal fossa without damaging the perineurium and wrapped loosely, with a 3-0.5 cm² strip of oxidized regenerated cellulose; previously soaked in 200 μl of a 0.1% rat serum albumin (RSA) in saline solution containing 200ng gp120-MN or for sham controls 0.1% RSA in saline. Then nerve was gently manipulated back into place and incisions closed with 4/0 sutures. Animal shows mechanical hypersensitivity on day 14 and it persists for 43 d [53, 55]. There is enhanced mechanical hypersensitivity by combining...
perineural HIV gp-120 and didanosine [50 mg/kg in saline] at the time of surgery and three times a week thereafter for a maximum of 3 w [58].

Antiretroviral drug-induced sensory neuropathy
The prevalence of peripheral neuropathy has increased among HIV/AIDS patients with the greater use of nucleoside reverse transcriptase inhibitors (NRTIs), particularly zalcitabine (d4T), stavudine (d4T) and didanosine (ddI), leading to the recognition of the disorder, termed antiretroviral toxic neuropathy (ATN).

Antiretroviral toxic neuropathy (ATN) model
In this, there is a combined ex vivo and in vivo models of ATN-induced by didanosine (ddI) following inoculation of the lentivirus, feline immunodeficiency virus (FIV). Briefly, Specific pathogen-free neonatal (day 1) kittens are infected with 0.2 ml of infectious (10^4 TCID_{50}/ml) or heat-inactivated virus in accordance with CCAC guidelines, as described previously [59]. FIV-infected and mock-infected animals are treated with ddI (33 mg/kg daily) by oral gavage starting at 6 w post-infection until 12 w post-infection. This treatment causes axonal injury and associated neuro-behaviour changes. ddI mediates ATN through mitochondrial injury in neurons. The FIV strain used in this study was an infectious neuroviral recombinant molecular clone, V1-Ch, derived by transfection of CrFK cells and amplification in feline peripheral blood mononuclear cells (PBMCs), as described previously. Culture supernatants from FIV-infected feline PBMC, which serves as source of infectious virus for these experiments, were cleared of cellular debris by centrifugation and titered by plaque assay at 6 w post-infusion to understand the pathogenesis of neuropathy. Important pathogenic mechanisms still remain active and unmodified by the treatment [59].

CONCLUSION
During the past few decades, the use of animal models has open vistas to understand the pathogenesis of neuropathy. Important pathogenic mechanisms still remain active and unmodified by present therapeutic strategies. So, this update will help to explore new therapeutic interventions in the management of NP.

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CONFLICT OF INTERESTS
Declared none

REFERENCES


