



Cellular and Molecular Machinery of Neuropathic Pain: an Emerging Insight

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Abstract

Purpose of Review Neuropathic pain (NP) has been ubiquitously characterized by lesion and its linked somatosensory system either the central nervous system (CNS) or peripheral nervous system (PNS) This PNS episode is the most prevalent site of NP origin and is found to be associated with afferent nerve fibers carrying pain signals from injured/trauma site to the CNS including the brain. Several kinds of pharmacotherapeutic drugs such as analgesics, anti-convulsants, and anti-depressants are being employed for the its possible interventions. The NP has been a great interest to follow different pathophysiological mechanisms which are often considered to correlate with the metabolic pathways and its mediated disease. There is paucity of knowledge to make such mechanism via NP.

Recent Finding Most notably, recent pandemic outbreak of COVID-19 has also been reported in chronic pain mediated diabetes, inflammatory disorders, and cancers. There is an increasing incidence of NP and its complex mechanism has now led to identify the possible investigations of responsible genes and proteins via bioinformatics tools. The analysis might be more instrumental as collecting the genes from pain genetic database, analyzing the variants through differential gene expression (DEG) and constructing the protein–protein interaction (PPI) networks and thereby determining their upregulating and downregulating pathways.

Summary This review sheds a bright light towards several mechanisms at both cellular and molecular level, correlation of NP-mediated disease mechanism and possible cell surface biomarkers (receptors), and identified genes could be more promising for their pharmacological targets.

Keywords Neuropathic pain · Pharmacological targets · In vivo models · In vitro models COVID-19 · Na/K ion channel · CIRD · DEG

Introduction

NP has been known as a pain caused by lesion or diseases affecting the somatosensory system, which then interferes with the perception of touch, pressure, and pain and arises from different parts as joints, muscles, and fascia, including various sensory receptors [1]. At a global level, it has been highlighted as approximately 7–10% and varies at various mechanical and hyperalgesia degrees [2]. The onset of NP is mostly related with metabolic disorders such as diabetes, viral infection-linked neuropathies, and autoimmune and inflammatory disorders including rheumatoid arthritis [3,••]. It has been investigated that any damage to the peripheral nerves results in peripheral neuropathic pain and has been associated with AIDS, multiple sclerosis, stroke,

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and other chronic disorders, whereas central neuropathic pain arise from CNS injury [4]. The prognosis of NP could be performed by screening for reflexes, sensory, and motor function via imaging techniques as MRI, CT, and X-rays [5, 6].

In recent years, available pharmacotherapy against neuropathic pain has been categorized into four major lines as first-line interventions used as serotonin-noradrenaline inhibitor (e.g., pregabalin drug), second-line interventions that allows a regulated opioid release, third-line treatment as cannabinoids, and fourth-line treatment as botulinum toxin, methadone [7.●]. Such medications and/or therapy are more capable to target receptors including neuroimmune cells triggers the pain as a result of immune response. In 2019, Oliveira-Fusaro reported that NP initiation and maintenance require crucial signaling from microglia to neurons that is critically linked with the upregulation of P2X4 receptor [8.●●].

In addition, RNA research has been focused on differentially expressed mRNA and miRNA and has reported the genes CXCR2, GRK1, IL12B, and TNFSF8 are involved in the pathogenesis of NP [9]. Owing to genetic abnormalities or mutations, very limited cases of NP are reported at clinical level. For example, Fabry disease has been known for the mutation in the X-chromosome and imparts its more effects on males at higher rate than the females [10]. Unlike targets identification, release of inflammatory and/or cytokines

have also contributed to peripheral nerve damage. These NP mediated cytokines could also considered as both pro- and anti-inflammatory molecules. Promisingly, displayed to be the crucial players for triggering pain and its mediated activated immune machineries (Fig. 1) [11].

Several animal and/or rodent models have shown a great interest for pain researches and utilized for the possible drug-targeted therapies in NP mechanism at both PNP and CNP systems. These experimental research models have also been implied to enquire the efficacy of the developed pharmacological drugs/molecules for therapeutic interventions as either non-invasive or non-pharmacological stage [12.●]. This review will provide an insight and shed a bright light on the available treatment options for neuropathic pain in mediated COVID-19 infections and other complications at both pre-clinical and clinical platform.

Characterization and Mechanistic Episodes of NP

Due to lesions in the spinal cord and/or brain, central neuropathic pain could be an integral action linked with syringomyelia and demyelinating diseases. In contrast, the unmyelinated C fibers have been considered as small in size and myelinated A fibers including A β and A δ fibers have also been known to play a key role in the pathology of peripheral

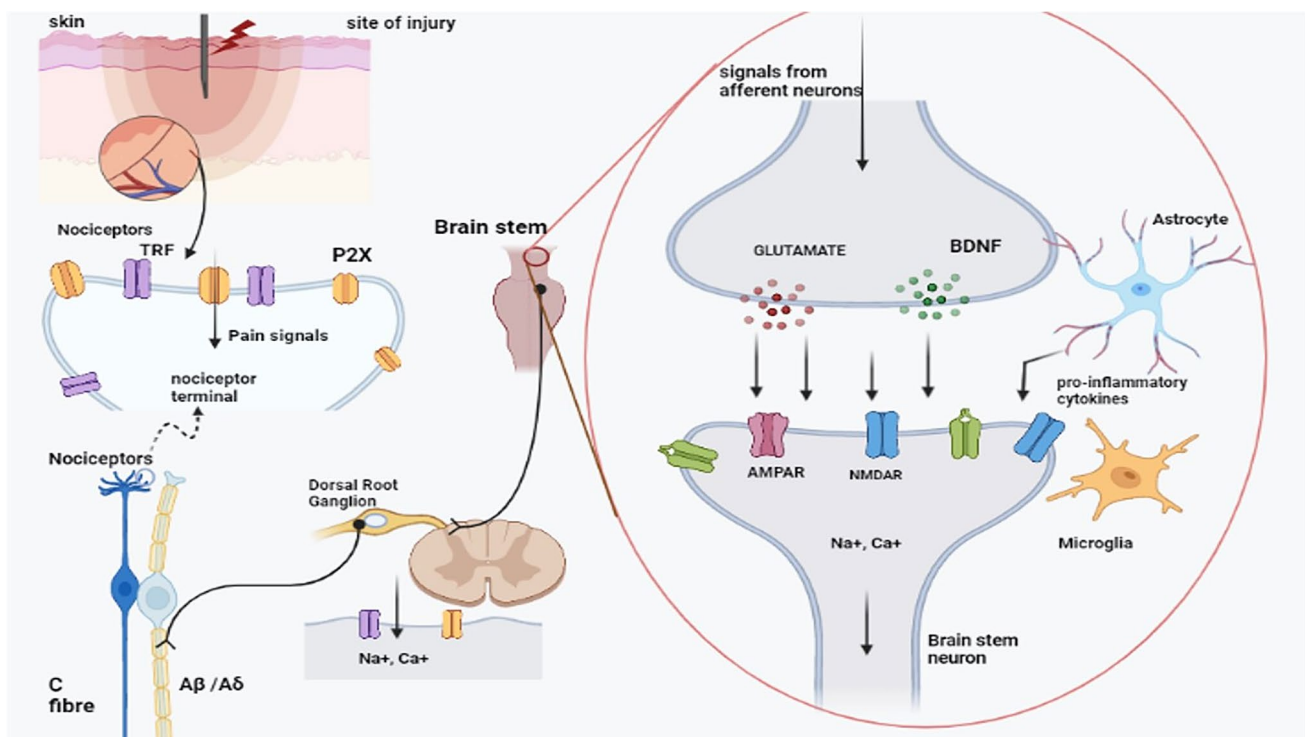


Fig. 1 Pain signaling episodes of brain injury

neuropathic pain. Such fibers have been recognized as sensory fibers [1]. Both central and peripheral neuropathic pain arise at the site of skin with abnormal sensation. Sensory fibers have been considered for diagnostic approach and critically linked with both positive and negative sensory symptoms in patients. In addition, pain has been detected maximally at particular site via increased mechanical hypersensitivity and reduced hypersensitivity to thermal sensation as heat and cold. Altered and disoriented sensory signal transmissions are the resultants of affected nerves with alterations in their ion channels which includes, increased sodium ion channel activity enhancing the excitability and poor fluxes of potassium ions [13]. The nociceptive signaling has also been influenced by the tunneling release of neurotransmitters that are mediated by voltage-gated calcium channel (VGCC) and any dysregulation and/or dysfunction to the voltage-gated sodium channels (VGSC) also raised the sodium ion channel activity and thereby resulting hyperalgesia with non-painful stimuli [14]. This electrifying potential is needed to activate VGSC that is mediated by the interaction of pain stimuli molecules to the transient receptor potential (TRP). It has also a major concern for mechanical stimuli. Under pathological/physiological conditions, such kind of stimuli could show an activation of TRPA1 and TRPV4. It has also observed that both hot and cold temperature triggered thermal stimuli are more capable to activate TRPA1, TRPM8, and TRPV1 respectively (Fig. 2) [15].

It has been implicated that any painful sensation or pain induced by any pathological condition alters the microglia and astrocyte function which then further modify the spinal microenvironment and therefore causing the release of soluble neurotransmitter molecules. Such molecules or neurotransmitters are able to show nociceptive neuronal excitation and helps for the excitation of Na^+ channel excitation

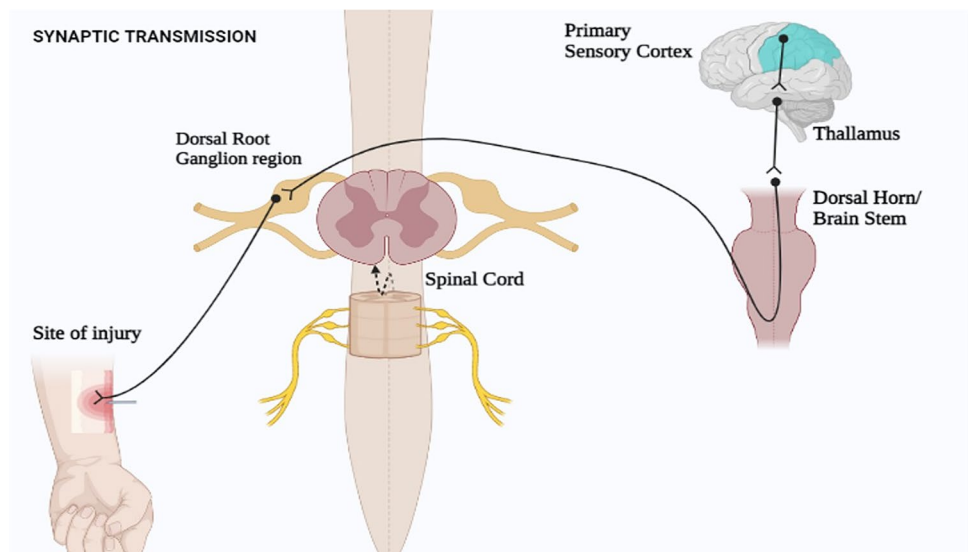
[16]. Additionally, an injury to the peripheral afferent nerves or peripheral axotomy causes invasion of immune cells at the juncture of dorsal root ganglions (DRGs). These actions have shown an extended release of cytokines and multiple alterations in gene expression, thus considering as the primary site of neuropathic pain at the injury site [17]. The chemokines which set a positive feedback loop in neuroinflammatory signal cascade are CCL2, CX3CL1, and CXCL1 [18.●●]. The persistent changes in the gene expression have also found with an involvement of neuroimmune interactions. Some of the recognized genes involved in neuropathic pain are III1 receptor antagonist (III1rn and other immune genes [19]. Once the P2X (P2X1, P2X2, P2X3, P2X4, P2X5 P2X6, and P2X7) receptor binds with ATP, opening of pore cascade initiated to produce purinergic signaling at patho/physiological consequences). Therefore, the upregulation of P2X4 triggers the release brain derived neurotrophic factors (BDNF) causing variation in membrane anion gradient in NP [20].

NP-Mediated Inflammatory Diseases and Its Pharmacological Interventions

Diabetic Neuropathy

Diabetic peripheral neuropathy (DPN) is commonly represented as distal symmetric polyneuropathy (DSPN) and the foremost neuropathy distributed at global level [21]. Sensory, autonomic, and motor axons are the preferred targets in the neurodegenerative diseases of the PNS. Axon-Schwann cell interaction is essential for maintenance of axon-cytoskeletal structure. It has been depicted that any damage to the Schwann cell results in axonal degeneration.

Fig. 2 Mechanistic action of synapse in pain signals



Importantly, mononucleotide adenylyltransferase has been regarded as crucial player for diabetic neuropathy mechanisms [22]. Blood-nerve barrier (BNB) has been known for maintaining the intact parts of nervous system. Any damage due to injury or pathological condition may alter the delicate BNB drastically and caused high permeability in BNB and considered as the first reported step for development of diabetic neuropathy [23.●]. Reports have also published on other regulators (glucose and insulin) for controlling the multiple cellular processes in brain. Both the hypoglycemic and hyperglycemic conditions could also show diabetic neuropathic pain (DNP) modulation in the central nervous system [24].

Cancer

Neuropathic cancer pain has also shown an increasing recognition and displayed either primary tumor/metastases or due chemotherapeutic interventions that affects the nervous system. The primary state of such conditions occurs due to the infiltration of tumor to the different parts of the PNS or CNS [25]. At the initial stage, the tumors would infiltrate the nerves thereby disrupting the neuronal transmission. This is accompanied by the inflammation and further infiltration mediated differentiation in nerve cells [26.●]. Whereas in final stage, chemotherapy-induced neuropathic pain (CINP) has been shown a negative impact on PNS via chemotherapeutic drugs as paclitaxel, and oxaliplatin has been reported with major incidences [27]. Initial chemotherapeutic treatment produces acute pain followed by repetitive treatment cycles to cause chronic neuropathic pain [28].

Chronic Inflammatory Rheumatoid Diseases (CIRD)

Rheumatic disease has been revolutionized and/or characterized by fibromyalgia and considerably involves inflammatory pain which leads to the impaired function of cellular systems. It has been evidenced that rheumatic diseases chronic episodes as rheumatoid (RA), psoriatic (PsA), and spondyloarthritis (SpA), where SpA is reported to have high prevalence of neuropathic pain [29]. The detection of such CIRD has put to enquire Pain DETECT questionnaire [30] and DN4 questionnaire [31]. On the contrary, fibromyalgia was shown with a lack of lesions in the somatosensory system while similar to central neuropathic pain (CNP) and has been reported with the modulation in the levels of neurotransmitter signaling and thereby causing small fiber neuropathies [32.●].

Central Post-Stroke Pain

Central post-stroke pain (CPSP) is a chronic neuropathic pain due to CNS damage characterized by dysfunction of

spinothalamic tract (ascending pathway that transmits pain, temperature, and senses from spinal cord), central sensitization, and pain network disinhibition [33]. The pathophysiology of thalamic pain syndrome with lesion in the CNS is complicated with contributions from cerebral cortex, opioid receptor, and long-chain fatty acid receptor GPR40 [34]. When it comes to the therapeutic intervention for CPSP drugs like pregabalin, gabapentin and amitriptyline and mirror therapy (MT) were preferred over physiotherapy which is less responsive [35.●].

Alzheimer's Disease and Neuropathic Pain

Alzheimer's disease (AD) is a cerebral cortex disease which is characterized by cognitive abnormalities and emotional dysfunction [36]. Patients with such cognitive abnormality may not be able to communicate their pain and seek proper treatment. The correlation study between chronic pain and AD has suggested pathologies like microglial activation, noradrenergic system abnormality, and increased central neuroinflammation [37].

Central Neuropathic Pain in Parkinson's Disease

The most common neurodegenerative disorder among the geriatric population is Parkinson's disease (PD); associated with motor dysfunction, it often remains unnoticed. James Parkinson describes the varying pain from early stage to advanced stage as Parkinson agitans which includes both neuropathic (radicular or articular) and nociceptive pain [38]. Chronic pain in PD is assessed using different questionnaires like Leeds Assessment of Neuropathic Symptoms and Signs, Brief pain inventory, and King's PD pain scale, which classifies the various pain and broadly categorize them as nociceptive, neuropathic, and miscellaneous pain [39].

Traumatic Brain Injury and Painful Episodes

External force or exposure to the head either due to direct blow or shock wave is known as traumatic brain injury (TBI) with an annual incidence of 50 million cases and the most prevalent being the mild TBH which affects 75–80% of the population which often resulted in chronic posttraumatic headache (PTH) [40, 41]. The pathophysiological investigations on the brains of patients who sustained TBI have revealed symptoms related to Alzheimer's, which is given as chronic traumatic encephalopathy. TBI occurs when the brain hits the surface of the cranium as a result of force applied, and this causes tearing of axons in the white matter, known as "diffuse axonal injury" [42].

Brain Tumors and Neuropathic Pain

The nerve which is infiltrated or compressed by tumor affects the nervous system directly and often leads to neuropathic cancer pain (NCP) [43].

COVID-19 Infection and Neuropathic Pain

In recent years, COVID-19 or human corona virus was found to be more neuroinvasive which then possibly could show axonal propagation. Such events have been symptomatically reported with muscular and joint pain followed by headache [44, ●●]. The invasion of this magic virus was enquired in biological fluid as CSF in COVID-19-infected patients and the confirmation of its presence could be detected by using RT-PCR. This manifestation has been progressive which could be due to the direct attack of virus on nervous system, due to parainfection (infectious agents affect the nervous system causing direct illness, meningitis) or post-infection at the time of recovery, where immunity has been compromised [45]. In the absence of an impaired electrophysiological state, small fiber-mediated neuropathies were observed in COVID-19-infected patients involving both the central and peripheral nervous system and have led to the suspect of neurotropism [46].

Biomarkers and Pharmacological Targets on Neuropathic Pain

Neuropathic pain has been investigated with its specific biomarkers and/or receptors pharmacological drugs. In 2018, Davis has reported the relationship between NP and epigenetics and conveyed message as neuropathic injury causes the abnormalities in miRNA expression and is capable to show downregulation of the potassium ion channels and glutamate transporters [47]. This has led the elevated expression of trophic factors including brain-derived neurotrophic factor. Clusters of miRNAs have also been established and considered via reduced expressions as miR-182, -183, and -96 in the dorsal root ganglions (DRG) of spinal nerve ligation (SNL) [48]. Epigenetic modifications have also been studied and made possible contributions with pain transition from acute to chronic state. One such modification is being conferred as DNA methylation in DRG due to peripheral nerve injury or SNL and has shown alterations in the expression of DRG gene [49]. Another epigenetic modification as histone methylation was also deciphered wherein the expression and/or levels of chemokines and mRNA modifications were raised in NP due to peripheral nerve injury.

On contrary, histone deacetylases (HDAC) were also reported to alleviate the neuropathic pain [50]. Neuronal injury or damage could also reported with the activation of peptidogenic or non-peptidogenic fibers or the peripheral

afferent fibers including A δ and C. This could be induced with the release of glutamate followed by the activation of G-protein coupled receptors (GPCR) that help to trigger the surrounding immune cells and could be considered as potential target [51]. In addition, synaptic transmissions are being mediated by the glutamate amino acid. This transmission episode could either be rapid or slow via its specific receptors as AMPARs or NMDARs, respectively. This scenario was reported and shown critical link between central sensitization and pain hypersensitivity [51]. It has been known that the most abundant and excitatory neurotransmitter was considered as glutamate and it has recognized on pain signaling cascades either via metabotropic or ionotropic factors. Unlike neurons, metabotropic glutamate receptors (mGluR) could be observed in glial cells prominently in astrocytes, microglia, and oligodendrocyte [52].

The glial cells have been implicated as immune cells in the central nervous system. In male population, the neuropathic pain was predominantly caused by microglia and on the contrary, female population, pain was observed due to the infiltration of T-lymphocytes [53].

In neuropathic pain animal model, several genetic markers have also identified and critically linked via genome-wide association investigations. It has also been reported that the genes could involve in neuropathic pain and thereby interrelated with metabolic process and ion channels. Several kinds of genes including MPZ, PRKCA, GCH1, COMT, and SCN11A have been identified in neuropathic studies in *in vivo* research models [54]. Another investigation has contributed to human pain genetics database and evidenced the variants single gene associated with monogenic disorders. These disorders have been recognized with pain machinery components as erythromelalgia wherein a variant gene SCN9A was reported to modulate the DRG electrophysiological properties [55]. In 2017, Chen and his co-workers have conducted one study and suggested that the non-injured or normal dorsal root ganglions adjacent to the injured and/or impaired DRGs could be contributed to the neuropathic pain. On this platform, the genes and their specific signaling cascade could be involved wherein FoxO played a key role for cell maintenance, Ctnnb1 for Wnt signaling, and Wt1 DEG and PPI networks.

In Vitro Research Models for Neuropathic Pain

Peripheral sensory neurons (PSN) are responsible to discriminate the different senses as they are heterogeneous in population. Direct collection of human PSN is not possible, so they are derived from human embryonic stem cells using the small molecule inhibition method. As they are believed to mimic the *in vivo* pathophysiology, they are used in *in vitro* peripheral nerve injury study [56]. Human fibroblasts were reprogrammed to nociceptor neuron (first order

pain sensory detection pathway) using different transcription factors like *Ascl1* and *Brn2* which generate neuron of generic type. Nociceptor neurons further develop into neuropathic pain and become sensitive to chemotherapeutic drugs or inflammatory mediators like cytokin [57]. The therapeutic drugs developed to treat peripheral nerve injuries (PNI) are subjected to in vitro model screening which uses excised spinal column from Sprague Dawley rats for dorsal root ganglion (DRG) neurons [58]. Engineering an in vitro model for CNS is difficult because of the lack of pathophysiological information like twist, compression, and physiological resemblance, which is overcome by 3D neuronal-glia model that mimics human head injuries mainly TBI and other CNS diseases [59].

In Vivo Research Models for Neuropathic Pain

Seltzer Model

In 1990, Seltzer and his co-workers have pointed out and revealed an excellent behavior model for evaluating neuropathic pain deficit in rats and considered for partial sciatic nerve injury [60]. This modality is based on a ligation at the juncture of the ipsilateral sciatic nerve. This nerve could be detected at hind paw of the experimental rats. Within few hours of partial sciatic nerve injury, the experimental rats could show allodynia, whipping, instinctive pain, and hyperalgesia. These kinds of behavior were observed at both (thermal and mechanical) the ligation process.

Spinal Nerve Ligation at L5/L6 Position

This model has not been deciphered yet at proper stage. It has been considered as an easy technique to perform L5/L6 ligation. The experimental rats could behave and depict a prolonged signals of both mechanical allodynia and hyperalgesia. Some reports have suggested and speculated for its consideration of modality in mice.

Axotomy model

This technique is well recognized and more considerable model for provoking neuropathic pain. It has also been used to poke a transection at the entire sciatic nerve present at the mid region of hind paw. In this techniques, the targeted sciatic nerve is dislocated from the connective tissue. Furthermore, a tight ligation is done by a nylon made suture that should be in a proximity at a juncture of both tibial and peroneal ways. This can be located with a gap of 1 cm. The nerve is therefore perfectly transected at the surrounded environment of suture invoked ligatures.

Spared Nerve Injury

This is also a more advanced neuropathic pain animal model established by Decosterd and Woolf. In this particular model, the experimental animals and/or rats were anesthetized followed by the dissection via biceps femoris muscles. In context of the spared nerve injury, sciatic nerve and its considered terminal branches as sural, common peroneal, and tibial were targeted. Thereafter, the tibial along with common peroneal nerves was tightly ligated and thereby ensured with an axotomical episodes at a distance of 2 mm on distal nerve juncture.

Pharmacological Guidelines and Treatment for NP

For the past decade, the European Federation of Neurological Societies (EFNS) has announced the primary guidelines on pharmacological intervention against neuropathic pain. The management of NP highlights on targeting the symptoms and limited only in some of the pathological condition. There is one recent report based on drug effectiveness wherein a particular intention on NP was proposed gabapentinoids and tricyclic antidepressants (TCAs), and serotonin–norepinephrine reuptake inhibitors were considered as first-line drugs against NP. In addition, lidocaine, capsaicin, and tramadol have been suggested as the second-line treatment, while morphine and oxycodone and botulinum toxin-A were recommended as third-line treatments for neuropathic pain in peripheral. Likewise, gabapentin and pregabalin were also approved by FDA for the therapeutic intervention of NP.

Spinal Cord and Traumatic Brain Injury-Mediated Pain Mechanism

TBI has been linked with both acute and chronic pain in animal models and humans. At initial stage, trauma evokes a somatic pain and considered as secondary injury machinery. This has made a possible contribution for both visceral and neuropathic pain. Pharmacological pain management immediately following experimental TBI in animal models can influence post-injury outcomes (Table 1). In addition, several animal models mimic SCI mediated pain. The spinal cord may be damaged directly via contusion, surgical lesions of the cord, and neurotransmitter-provoked excitotoxicity. Such kind of spinal cord models could be resulted as in mechanical and thermal (heat and cold) hyperalgesia.

Therapeutic Interventions Against Neuropathic Pain and Its Management

Several therapeutic strategies are developed for the treatment and management of neuropathic pain. The pharmacological

Table 1 Different rodent models for brain injury

Rodent model	Description
Weight drop injury	Considerable weight is dropped onto head held with one metal base. For this, scalp incision may be required
Impact acceleration injury	Considerable weight is dropped onto head held by foam pad. For this, scalp incision may be required
Fluid percussion injury (FPI)	Fluid pressure pulse applies mechanical forces onto exposed brain region either laterally or centrally. For this model, craniectomy may be required
Penetrating injury	One projectile is propelled into the brain region resulting in a focal injury. For this model, craniectomy may be required
Blast injury	Considerable compressed gas applies pressure wave, leading to a diffuse injury. Limited surgical preparation is required
Controlled cortical impact (CCI)	Computer controlled piston drives into cortex, creating a focal injury. For this model, craniectomy may be required

interventions are classified into three different categories based on their activity like serotonin uptake inhibitors, TCAs, opioids, and antiepileptic drugs. The identification of several biomarkers is found to be promising for future biomarker-based pain therapy which requires correlation-based information on biomarker and pharmacological effect, yet it is still time consuming and expensive. Non-pharmacological interventions are often non-invasive and the different therapies include mirror, cognitive behavior, adjunctive, and animal-assisted [61]. Non-destructive method followed after the failure of traditional treatments includes radio frequency (RF) approach which is categorized into pulsed and continuous RF of which pulsed RF is the most preferred as they modulate the pain signals instead of blocking them [62].

Conclusion

Neuropathic pain is chronic and has an increasing importance to enquire the negative impacts in population at global level. A diverse range of pathophysiological mechanism is being interconnected with other metabolic pathways in disease state. Considering the recognition of neurological disturbances in COVID-19 infections, we also convey a message that COVID-19-infected patients always have complaints for neuropathic pain. The exact mechanism of neuropathic pain is yet to be discovered, many pharmacogenomics studies and bioinformatics analyses are being deciphered, and several genes and proteins are also in debate for the identification and targets the patients with personalized medicines. Animal model development has also raised an understanding for pain and its linked mechanisms. In addition, pain models owing to pharmacological drugs and other diseases medications have also been recognized with better consideration of their pathophysiology and management.

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Consent for Publication All the authors have given the consent to publish.

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