3. Review of Literature
Pain according to International Association for the Study of Pain (IASP) is an unpleasant sensory and emotional experience associated with actual or potential tissue damage (Merskey and Bogduk, 1994). Pain can be essentially divided into two broad categories: adaptive and maladaptive. Adaptive pain contributes to survival by protecting the organism from injury or promoting healing when injury has occurred; it is not a disease. Maladaptive pain is an expression of the pathologic operation of the nervous system and represents pain in a diseased state (Woolf, 2004). Based on duration, pain is divided into two main categories: acute and chronic pain. Acute (nociceptive pain) is part of a rapid warning signal and relays instructions to the motor neurons of the central nervous system to minimize detected physical harm. The acute pain is mediated by nocicepters located on A-δ and C fibers. Chronic pain, however, serves no biologic function as it is not a symptom of a disease process but is a disease process itself. From pathophysiological point of view, pain can be classified as physiological (somatic and visceral pain), and clinically relevant pain (inflammatory, neuropathic, idiopathic pain and psychogenic pain (Ripamonti and Bandieri, 2009).

IASP defines neuropathic pain as “pain initiated or caused by a primary lesion or dysfunction or transitory perturbation in the peripheral or central nervous system” (O’Connor and Dworkin, 2009). Neuropathic pain is caused by an inappropriate response of the nervous system to non-noxious or noxious stimulation and may be initiated by a wide range of disorders, including: Trauma to the peripheral or central nervous system as seen with nerve entrapment, amputation, crush injuries & spinal cord injuries, infection from postherpetic or HIV associated neuralgia, pressure due to growth, as in neoplasia, as in compression, as in carpal tunnel syndrome, metabolic disturbances such as diabetic neuropathy, or uraemia, or ischaemia, as with infarct or stroke (Henry et al., 2007; Connor and Dworkin, 2009; Deger et al., 2011). Depends upon location the neuropathic pain has been categorized into peripheral and central neuropathic pain (IASP, 2010). Carpal tunnel syndrome (CTS), complex regional pain syndrome (CRPS), polyneuropathy, radiculopathy, postherpetic neuralgia, postsurgical neuralgia, nerve trauma and trigeminal neuralgia are some examples of peripheral neuropathic pain. Epidemiological studies of peripheral neuropathic pain have shown the incidence of polyneuropathy about 26% in type 2 (NIDDM) diabetic melitus (IASP, 2010). The 37 percentage of patients with prolonged low back pain have been shown to develop Radiculopathy. Around 10 % patients with herpes zoster infection have been reported to acquire postherpetic neuralgia. It has been demonstrated that incidence of postsurgical neuralgia is around 40% after
breast cancer surgery. The incidence of trigeminal neuralgia is around 27/100,000 person per year. Stroke, multiple sclerosis, spinal cord injury, and phantom limb pain are few example of central neuropathic pain. Epidemiological studies of peripheral and central neuropathic pain is reported to be around 8% of stroke patients, 28% of multiple sclerosis, 67% is spinal cord injury and 1/100,000 person per year that of phantom limb pain (Torrance et al., 2006).

An understanding of neuropathic pain requires the understanding of those mechanisms that cause neuronal hyperexcitability despite a reduced or lost input to the nervous system. The afferent pain signal input reduced due to the nervous lesion, simultaneously begins the regeneration and disinhibition of secondary hypersensitivity. The changes giving rise to this hypersensitivity occur at molecular, cellular and clinical levels with different manifestations (Borsook et al., 2011). At the “molecular” level, formation of new channels, upregulation of certain receptors, downregulation of others, expression of novel receptors, and induction of new genes are some of the phenomena that contribute to hyperexcitability. At the “cellular” level, the translation of molecular changes is multiple, including spontaneous discharges in nociceptors, reduced threshold to depolarize cell bodies, an increased response to suprathreshold stimulation, recruitment of silent nociceptors, expansion of receptive fields, changes in cell phenotypes and, as a consequence of this, secondary changes in spinal cord and brain relay stations. At “clinical” levels it is now clear that a series of mechanisms are involved in generating neuropathic pain symptoms and signs and that there is no simple translation of each mechanism into symptoms and signs. An important clinical observation in neuropathic pain is the combination of sensory loss due to damage of transmitting pathways and the development of maladaptive neuroplastic changes in the nervous system resulting in e.g. pain and hypersensitivity in the affected area (Borsook et al., 2011).

A large number of randomized clinical trial of different interventions for various neuropathic pain conditions have been published over the past several years, but substantial gaps in the literature remain. For these reasons, under the auspices of the International Association for the Study of Pain (IASP), Neuropathic Pain Special Interest Group (NeuPSIG), an international consensus process that included a diverse group of pain experts was convened to develop evidence-based guidelines for the pharmacologic treatment of neuropathic pain. These guidelines were endorsed by the American Pain Society (APS), the Canadian Pain Society (CPS), the Finnish Pain Society (FPS), the Latin American Federation (LAF) of IASP Chapters, and the Mexican Pain Society (MPS)
(Dworkin et al., 2007). Additional consensus guidelines for the pharmacologic treatment of neuropathic pain were created simultaneously by the European Federation of Neurological Societies (EFNS) (Attal et al., 2010) and the Canadian Pain Society (Moulin et al., 2007). Based on the guidelines of NeuPSIG, EFNS and CPS the drug therapy for the management of neuropathic pain can be classified as (Table 1).

3.I. Conventional Drug Therapy of Neuropathic Pain

3.I.A. Anti-depressants

3.I.A.1. Tricyclic Anti-depressants (TCAs)

Tricyclic anti-depressants (TCAs) are among the first class of medications proven effective for chronic neuropathic pain (Gilron et al., 2009). Their efficacy has been repeatedly confirmed in multiple consecutive rigorously conducted randomized trials in patients with diabetic neuropathy and postherpetic neuralgia (PHN) (Saarto and Wiffen, 2010). The presence of depression is not required for the analgesic effects of these medications, although they may be particularly useful in patients with inadequately treated depression. The efficacy of these drugs has until recently been ascribed to noradrenergic and serotonergic reuptake inhibition (Baastrup and Finnerup, 2008). This activity occurs in supraspinal pathways and likely modulates pain through descending inhibitory pathways. Although amitriptyline blocks tetroxin sensitive receptor (TTX-R) channels, it is unclear to what extent voltage gated sodium channels (VGSCs) are involved in the efficacy of TCAs. Based on the data of placebo-controlled trials, the systematic reviews have supported the efficacy of TCA (Saarto and Wiffen, 2010).

TCAs are typically inexpensive and usually administered once daily. The most common side effects of TCAs include sedation, anticholinergic effects (e.g., dry mouth, constipation, and urinary retention), and orthostatic hypotension. Secondary amine TCAs (nortriptyline and desipramine) are preferred because they are better tolerated than tertiary amine TCAs (amitriptyline and imipramine) with comparable analgesic efficacy (Rowbotham et al., 2005). Amitriptyline in particular should be avoided in elderly patients. The decision to start a TCA should also consider the possibility of cardiac toxicity. Nortriptyline is associated with sinus tachycardia and increases ventricular ectopy in a randomized controlled trial (RCT) as examined in patients with a history of depression and ischemic heart disease (Finnerup et al., 2005).
Table 1. Classification of neuropathic pain management based on NewPSIG, CPS and EFNS guidelines.

<table>
<thead>
<tr>
<th>Category</th>
<th>Medication</th>
<th>Interventions</th>
<th>Medicine status based on guidelines</th>
<th>References</th>
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<tbody>
<tr>
<td>Anti-depressant</td>
<td>TCA (Nortriptyline, Desipramine)</td>
<td>1. It’s first class of medications proven to effective for chronic neuropathic pain. 2. It’s reported to produce some side effects i.e., sedation, blurred vision, weight gain, urinary retention.</td>
<td>PSIG - Ist line; CPS - Ist line; EFNS - Ist line for PPN, PHN and CP.</td>
<td>(Dunner et al., 2005; Dworkin et al., 2007; Moulin et al., 2007; Attal et al., 2010)</td>
</tr>
<tr>
<td></td>
<td>SSNRI (Duloxetine)</td>
<td>1. It’s potential pain relief in patients with painful DPN but other type of neuropathic pain under investigation. 2. It’s known to produce the minor side effects i.e., nausea and depression.</td>
<td>PSIG - Ist line; CPS - IInd line; EFNS – IInd line for PPN.</td>
<td>(Dunner et al., 2005; Dworkin et al., 2007; Moulin et al., 2007; O’Connor and Dworkin 2009; Attal et al., 2010)</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine</td>
<td>1. It’s potential pain relief of neuropathic pain at higher dose level. 2. It’s known to produce risk of withdrawal syndrome.</td>
<td>PSIG - Ist line; CPS - IInd line; EFNS - IInd line for PPN.</td>
<td>(Dworkin et al., 2007; O’Connor and Dworkin 2009; Attal et al., 2010)</td>
</tr>
<tr>
<td>Anti-convulsant</td>
<td>Gabapentin, Pregabalin</td>
<td>1. It’s rapid and potential pain relief property due to their quick onset of actions. 2. It’s also known to produce the sedation, dizziness and edema.</td>
<td>PSIG - Ist line; CPS - Ist line; EFNS - Ist line for PPN, PHN and CP.</td>
<td>(Moulin et al., 2007; Attal et al., 2010; Finnerup et al., 2010)</td>
</tr>
<tr>
<td>Topical medicine</td>
<td>Lidocaine</td>
<td>1. It’s used for the localized pain relief in patients with PHN. 2. It’s also produce erythema and localized rashes.</td>
<td>PSIG - Ist line for localized peripheral NP; CPS - IInd line for localized peripheral NP; EFNS - Ist line for PHN.</td>
<td>(Gammaitoni and Davis, 2002; Moulin et al., 2007; Attal et al., 2010)</td>
</tr>
<tr>
<td>Opioid agonists</td>
<td>Morphine, Oxycodone, Methadone, Levorphanol, Tramadol</td>
<td>1. It’s potentially relieving the pain in patients with DPN, PHN, and phantom limb pain. 2. It’s known to produce to the nausea, vomiting, constipation, drowsiness, dizziness and seizures.</td>
<td>PSIG - IInd line under clinical circumstances; CPS - IIIrd line; EFNS - IInd line for PPN, PHN and CP.</td>
<td>(Dworkin et al., 2007; Moulin et al., 2007; O’Connor and Dworkin 2009).</td>
</tr>
</tbody>
</table>
However, substantial percentage of patients do not respond favorably to treatment with TCAs, as is also true of the other medications recommended for the treatment of NP, with no more than 40–60% of patients obtaining partial relief of their pain. TCAs treatment did not differ significantly from placebo in RCTs of patients with HIV neuropathy, spinal cord injury, cisplatin neuropathy, neuropathic cancer pain, phantom limb pain and chronic lumbar root pain (Dworkin et al., 2010). An increased risk of myocardial infarction with TCAs compared to selective serotonin reuptake inhibitors (SSRIs) has been reported. Finally, a large, retrospective cohort analysis found an increased risk of sudden cardiac death at dosages of 100 mg/day or higher (Coupland et al., 2011). Taken together, these data suggest that the lowest effective dosage of a TCA should be used in all patients with NP, and that TCAs should be avoided in patients who have ischemic heart disease or an increased risk of sudden cardiac death. A screening electrocardiogram (ECG) is recommended before beginning treatment with TCAs in patients over 40 years of age (Coupland et al., 2011). TCAs should be used cautiously in patients at risk for suicide or accidental death from overdose. They can cause or exacerbate cognitive impairment and gait disturbances in elderly patients, and may predispose to falls. Toxic TCA levels may result if TCAs are administered together with medications that inhibit cytochrome P450 2D6, such as SSRIs. Starting doses of TCAs should be low, and the dosage should be titrated slowly until pain is adequately controlled or side effects limit continued titration. Although monitoring medication levels is not usually necessary, it may reduce the risk of cardiac toxicity at dosages greater than 150 mg/day. TCAs, i.e., amitriptyline and some anti-convulsants i.e., phenytoin, carbamazepine and oxcarbazepine are often the first-line therapy for neuropathic pain in humans (Lalwani et al., 2005). Potential adverse effects include ventricular arrhythmias, but these usually only occur at much higher dose rates (Veris-van Dieren et al., 2007).

3.1A.2. Selective Serotonin and Norepinephrine Reuptake Inhibitors (SSNRIs)

Duloxetine is an SSNRI that inhibits the reuptake of both serotonin and norepinephrine. It has demonstrated to provide pain relief compared with placebo in three clinical trials in patients with painful disabetic peripheral neuropathy (DPN), but it has not been studied in other types of NP. Duloxetine has a generally favorable side effect profile and dosing is simple. Nausea is the most common side effect, but it occurs less frequently if
treatment is initiated at 30 mg/day and titrated after one week to 60 mg/day (Dunner et al., 2005). As a new medication, there is limited long-term safety information and efficacy data are limited to studies. Venlafaxine is an SSNRI that inhibits serotonin reuptake at lower dosages and both serotonin and norepinephrine reuptake at higher dosages and alleviate the neuropathic pain (Yucel et al., 2005). Venlafaxine is available in both short- and long-acting formulations. Two-to-four weeks is often required to titrate an effective dosage, and patients should be tapered gradually from venlafaxine because of the risk of discontinuation syndrome (Sabljic et al., 2011).

3.1A.3. Selective Serotonin Reuptake Inhibitors (SSRIs)

The SSRIs citalopram and paroxetine showed limited evidence of efficacy in painful DPN (Finnerup et al., 2005). Bupropion, which inhibits the reuptake of norepinephrine and dopamine, was efficacious in various peripheral and central NP conditions (Finnerup et al., 2005). Based on the results of these trials, bupropion, citalopram, and paroxetine are options for patients who have not responded to an adequate trial of a TCA or SSNRI when additional treatment with a medication with analgesic and antidepressant effects is being considered.

3.1B. NMDA Receptor Antagonists

N-methyl-D-aspartate (NMDA) receptors (R) are involved in activity-dependent central sensitization after nerve injury. Antagonists of NMDARs have therefore been proposed as therapeutic agents for reducing neuropathic pain states (Zhou et al., 2011). However efficacy of NMDAR antagonists in neuropathic pain is still a question of controversy. A few early clinical trials with dextromethorphen (Non-selective NMDARs blocker) and mementamine (selective NMDARs blocker) have shown evidence of efficacy but later trials have provided limited and no evidence of efficacy (Zhou et al., 2011). Interestingly, another experimental study reports that the anti-allodynic effects of NMDAR antagonists outlast the duration of their NMDAR antagonism in rats with neuropathic pain (Swartjes et al., 2010). It was speculated that a short NMDAR blockade may downregulate the central sensitization triggered by nerve injury, resulting in a long-lasting anti-allodynic effect. Similarly, some human studies have observed long-lasting relief in patients with neuropathic pain who are treated with NMDAR antagonists (Zhou et al., 2011). Altogether,
preclinical and clinical studies suggest that a short exposure to NMDAR antagonists could give long-lasting relief to some cases of neuropathic pain (Swartjes et al., 2010).

Treatment of chronic neuropathic pain is difficult because central sensitisation has already occurred. As this is mediated through the NMDA receptor; hence an ideal medication should include an NMDA receptor antagonist. Ketamine non-competitively antagonizes NMDA receptors and is also suggested to impair excitability in superficial dorsal horn neurons by blocking sodium and voltage-gated potassium currents (Kiefer et al., 2008). Although it has proven benefit in the treatment of neuropathic pain (Uzaraga et al., 2011), systemic administration results in unacceptable side effects such as behavioural disturbances and neurotoxicity. The use of a topical mixture of 1% ketamine and 2% amitriptyline over 6–12 months provided adequate analgesia for neuropathic pain syndromes in people without side effect (Lynch et al., 2005). Dextromethorphan is a non-competitive NMDA antagonist which has analgesic and anticonvulsant properties but it has a short half-life, rapid clearance, and poor bioavailability in the dog so is unlikely to be useful (Karimi et al., 2010).

Agmatine is an endogenous substance recently identified in mammals and is widely distributed in a number of tissues including brain, stomach, intestine and aorta (Li et al., 2010). Agmatine is an endogenous amine and ionic cation; it is synthesized from L-arginine by the enzyme arginine decarboxylase (Haenisch et al., 2008). Agmatine is stored in neurons, released in a Ca^{2+} dependent manner by depolarization and is taken up by synaptosomes. Hence, agmatine is proposed to be a neurotransmitter in the brain (Uzbay, 2012). Agmatine antagonizes some hyperalgesic states without altering pain threshold e.g. as measured by tail-flick responses. Peripheral administration of agmatine results in an enhancement in the antinociceptive effect of co-administered morphine via a α2-adrenoceptor mediated mechanism (Li et al., 2011). Agmatine can generate a voltage- and concentration-dependent blockage of NMDA receptor channel (Ahmed et al., 2005) and it can competitively inhibit nitric oxide synthase (NOS) which catalyses the conversion of L-arginine to nitric oxide (NO) as well (Satriano et al., 2008). Agmatine decreases the neuropathic pain threshold in rats at a dose-dependent manner with no disturbance in the locomotor activity (Liu and Bergin, 2009). Given the large number of patients with neuropathic pain and the limited number of treatment options currently available, agmatine may provide an effective alternative therapy for relieving pain in such patients.
3.I.C. Anti-convulsants

Antiepileptic medications carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproic acid, gabapentin, pregabalin etc. can be considered options for patients who have not responded satisfactory to antidepressants and opioids. Several anti-convulsants have an anti-allodynic effect and are reported by human patients to be particularly effective for neuropathic pain that is burning and lancinating in nature (Buvanendran et al., 2010). Gabapentin (Neurontin, Pfizer) was originally developed as an anti-convulsant but clinically has been more useful for treatment of neurogenic pain in people (Waszkielewicz et al., 2011). It is thought to prevent the release of glutamate in the dorsal horn via interaction with the alpha2delta subunit of voltage-gated calcium channels (Finnerup et al., 2010). Pregabalin is emerging as an effective drug for neuropathic pain in humans. It is a structural, but not functional, analogue of GABA which is also thought to exert its pharmacodynamic effect by modulating voltage-gated calcium channels resulting in a reduction of glutamate and substance P release. In people the typical side effects are dizziness, somnolence and weight gain but acute psychosis and epileptiform EEG changes have also been reported (Olaizola et al., 2006). The anti-convulsants phenytoin, carbamazepine and oxcarbazepine are unlikely to be successful because of inappropriate pharmacokinetics (Alvarez et al., 1998).

3.I.D. Topical / Local Anesthetics

Topical preparation is recommended for patients with localized peripheral NP but not for patients with central NP. Clinical trials have demonstrated significantly greater pain relief with lidocaine patch 5% than with vehicle-controlled patches in patients with PHN and allodynia. The only side effect that occurs with the lidocaine patch 5% is mild skin reactions such as erythema and localized rash (Colvin et al., 2011). Blood levels are minimal with the approved maximum dosing of three patches/day applied for 12 h and also when four patches/day are applied for 18 h (Gammaitoni et al., 2002). The efficacy of lidocaine gel has been demonstrated in patients with PHN and allodynia, but not in patients with HIV neuropathy (Estanislao et al., 2004). The results of RCTs that compared topical capsaicin with
placebo in patients with painful DPN, PHN, and post-mastectomy pain have been found to be inconsistent (Finnerup et al., 2005; Anand and Bley, 2011).

3.I.E. Opioid Analgesics

Opioid analgesics have demonstrated efficacy in patients with a variety of peripheral and central NP conditions, including painful DPN, PHN, and phantom limb pain (Zin et al., 2010). However, morphine did not differ from placebo for chronic nerve root pain (Kim et al., 2011). These trials conducted with different opioids including oxycodone, morphine, methadone, and levorphanol indicated that the magnitude of pain reduction with opioid is as good as that obtained with other treatments for NP (Tessaro et al., 2010). Tramadol is weak opioid agonist that has been shown to inhibit the reuptake of norepinephrine and serotonin. The results obtained in patients with PHN, painful DPN, painful polyneuropathies of different etiologies, and post-amputation pain demonstrated that tramadol reduced pain and improved some aspects of health-related quality of life. Tramadol may be somewhat less efficacious than stronger opioid analgesics in patients with NP (Thorn et al., 2011). Opioid analgesics are generally considered a second-line treatment for several reasons. First, in head-to-head comparisons, opioids have produced side effects more frequently than TCAs and gabapentin (O’Connor and Dworkin, 2009; Dworkin et al., 2010), and some of these side effects can persist throughout long-term treatment (Watson et al., 2004). Second, the long-term safety of opioid treatment has not been systematically studied and evidence that long-term opioid use is associated with the development of immunologic changes and hypogonadism (Elliott et al., 2011). Third, experimental data suggest that opioid treatment can be associated with hyperalgesia and opioid induced hyperalgesia could potentially alter the risk benefit ratio of long-term therapy in patients with various types of acute and chronic pain. Finally, the results of recent studies using a variety of methods and patient samples have provided estimates of the frequency of opioid analgesic misuse or addiction that range widely from less than 5 % to as much as 50 % (Ballantyne and LaForge, 2007). First-line use of opioids should be reserved for circumstances in which suitable alternatives cannot be identified and should be on a short-term basis (Ballantyne and LaForge, 2007). In selected clinical circumstances, opioid analgesics and tramadol can also be considered for first-line use. As for opioid analgesics,
Tramadol is recommended primarily for patients who have not responded to the first-line medications but it can also be considered for second-line use in select clinical circumstances (Bohlega et al., 2010).

There are a number of other medications that would generally be regarded as third-line treatments but that could also be used as second-line treatments in some circumstances (e.g., when treatment with an opioid agonist is not indicated or when the patient’s treatment history suggests greater potential for their effectiveness) (Fig. 1). This medications is substantially reported to have less evidence of efficacy than exists for TCAs, SSNRIs, calcium channel α2-δ ligands, topical lidocaine, opioid analgesics, and tramadol including certain other anti-epileptic (carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproic acid), anti-depressant (bupropion, citalopram, paroxetine) medications, mexiletine, N-methyl-D-aspartate (NMDA) receptor antagonists, and topical capsaicin (O'Connor and Dworkin, 2009).

3.II. Current Development in Drug Therapy of Neuropathic Pain: Experimental & Clinical Evidences

The presently clinically employed pharmacotherapy of neuropathic pain is complex with marginal efficacy. There is a need of newer agents to combat the neuropathic pain of diverse etiology. Experimental studies have projected many key targets that may be manipulated to yield potential anti-nociceptive agents. Though the role of these targets has been studied individually, yet these targets may be interlinked and may activate or inhibit one another to produce neuropathic pain (Fig. 2).
Fig. 1. Current clinical therapeutic options for the management of neuropathic pain.

- **Non opioids**
  - (Paracetamol, NSAIDs)
- **Weak opioids**
  - (Tramadol, Codeine)

**Neuropathic Pain**

**First line therapy**

- **TCAs**
  - (Amitriptyline, Nortriptyline, Lofepramine)
- **Anti-convulsants**
  - (Gabapentin, Pregabalin)
- **Topical Agent**
  - (Tramadol, Codeine, Dihydrocodeine)

**Second line therapy**

- **Another TCAs**
  - (Trazodone, Venlafaxine, Duloxetine, Mirtazapine, Bupropion)
- **Anti-convulsants**
  - (Carbamazepine, Topiramate, Lamotrigine, Clonazapam)
- **Strong opioids**
  - (Morphine, Oxycodone, Buprenorphine, Fentanyl, Methadone)

**Third line therapy**

- **NMDA antagonist**
  - (Ketamine)
- **Anti-arrhymic agents**
  - (Lidocaine, Mexiletine, Flecainide)

**Response**
- (Continue therapy)
- (Continue 1st line therapy)
- (Continue 2nd line therapy)
- (Continue 3rd line therapy)

**No Response**
Fig. 2. Diagrammatic representation of inter-relationship of different targets responsible for development of neuropathic pain and subsequently possible therapeutic options for its effective management.

In the pathological conditions, the development of neuropathic pain may be mediated through various neuronal cell structural and functional abnormalities via modulation of cellular membrane mediated functions such as ion transporters (NKCC, and glycine); ion channels (Na⁺, Ca²⁺, K⁺, and TRP channel); ion exchangers (NCX, and NHE); receptors (histamine, 5HT-1A, dopamine, alpha and beta-adrenergic, EAA, NP, MC-4, PR, σ-opioid, ORL-1, PAR, Eph B, endothelins, kinin-B, and RAGE); growth factors (cytokines, FGF, IGF, and EDGF); and other ligands (neurotrophic factor, CAM, Cytokines, and AGE). The above
changes may modulate the cytosolic ionic pool (Na\(^+\), Ca\(^{2+}\), K\(^+\), and H\(^+\)); radical pool (O\(^-\), NO, and NOO\(^-\)); and the enzymatic pool (COX, LOX, kinases, MMP, protease, phosphatase, VP, AR, SDH, FAAH, D-amino acid oxidase). These cytosolic changes may change the expression of various toxic proteins such as complement cascades, TNF-α, abnormal ion channel proteins, pro-inflammatory and pro-apoptotic proteins that in turn induce neuronal sprouting, hyper-sensitization of neuronal nociceptors, activation of neuronal immune and immune like cells such as glial cells.

3.II.A. Non-steroidal Anti-inflammatory Drugs (NSAIDs)

The prevalent belief that non-steroidal anti-inflammatory drugs (NSAIDs) lack efficacy for the treatment of neuropathic pain is so widely accepted that current neuropathic pain treatment guidelines either do not mention this class of medications or simply state that evidence of efficacy is limited or lacking (Attal \textit{et al.}, 2006; Moulin \textit{et al.}, 2007). There are several possible explanations for the striking discrepancy between the widespread use of NSAIDs by patients with neuropathic pain and the apparent consensus among pain specialists that these medications lack efficacy for neuropathic pain. First, it is possible that NSAIDs actually are efficacious for neuropathic pain but that this has not been recognized because of few clinical trials. In addition, it is recognized that many individuals with neuropathic pain have mild pain and can be managed by their community physicians without prescription medications or they find non-prescription analgesics are sufficient. It is possible that such mild pain responds to NSAIDs, but that moderate-to-severe neuropathic pain does not. In studies of two different models of radiculopathy, systemic, intrathecal, or epidural administration of a COX-2 inhibitor has been demonstrated to reduce mechanical hypersensitivity (Reuben \textit{et al.}, 2006). In a rat model of pain associated with varicella-zoster virus infection, ibuprofen reversed mechanical hypersensitivity (Rutten \textit{et al.}, 2011). Further, the administration of COX inhibitors i.e., ketorolac (non-selective COX-1 inhibitor) and NS-398 (selective COX-2 inhibitor) have been shown to attenuate partial sciatic nerve ligation (PSNL) induced mechanical hypersensitivity in rats (Yang \textit{et al.}, 2009). The topical administrations of NSAIDs and aspirin have also been documented to attenuate herpes zoster induced PHN in patients (Dworkin \textit{et al.}, 2010).

3.II.B. Corticosteroids

Corticosteroids are believed to provide long-term pain relief because of their ability to inhibit the production of phospholipase-A-2 and to inhibit the expression of multiple
inflammatory genes coding for cytokines, enzymes, receptors and adhesion molecules (Skedros and Pitts, 2008). The local application of corticosteroids i.e., betamethasone has been shown to be effective in L₆ nerve root compression and decompression-induced neuropathic pain by reducing the level of dorsal root ganglion substance P expression in cat (Wong and Tan, 2002). The topical application of corticosteroids has been shown to reduce the trigeminal nerve injury-induced peripheral neuropathic pain in rat (Robinson et al., 2004). The chronic treatment of corticosterone and dexamethasone have been documented to reduce nociceptive pain sensation by alteration of neuropeptide expression and nociceptive pain signal transmission in rats (Pinto-Ribeiro et al., 2009). The oral and intrathecal administration of methylprednisolone have also been reported to reduce the postherpetic neuralgia and siatic nerve injury mediated neuropathic pain (Candido et al., 2011). Clinically, the intrasacral (between S₁-S₃) administration of methylprednisolone has been documented to reduce the sciatic nerve injury-induced neuropathic pain (Fashner and Bell, 2011). The administration of corticosteroid triamcinolone acetonide at near the lumbar ganglion has shown to reduce the SNL-induced sympathetic nerve sprouting, mechanical pain behavior, spontaneous bursting activity, cytokine and nerve growth factor production associated neuropathic pain development in rat (Li et al., 2011a). Corticosteroids are also reported to have an effect in sympathetically mediated pain and decrease substance P expression (Pinto-Ribeiro et al., 2009; Li et al., 2011).

3.II.C. Ion Channel Blockers and Modulators

3.II.C.1. Calcium Channel Blockers

Voltage gated calcium channels (VGCCs) are known to modulate nociceptive transmission at the level of the neuronal synapse in the central nervous system. The role of the L, N, and P/Q type VGCCs varies with the nature of neural injury (Cao, 2006). One indication of the important role played by these channels is the dense expression of the N-type channels in the superficial laminae (I, II) of the dorsal horn, the site of synapse for first-order primary afferent neurons. With depolarization, there is an influx of Ca²⁺ ions into neurons and release of neurotransmitters such as glutamate, and norepinephrine etc. Perineural administration of Ca²⁺ channel blockers inactivates N-type Ca²⁺ channels. Intrathecal delivery of antagonists VGCCs show that blockade of N, P/Q, and L type channels reduces pain, allodynia, and
hyperalgesia (Cao, 2006). The intrathecal and oral administration of cilnidipine has been reported to produce anti-nociceptive effect in mice (Koganei et al., 2009). A growing body of evidence points to a distinct pattern of Ca\(^{2+}\) channel subunit expression in animal models of chronic neuropathic pain (Bauer et al., 2009). Peripheral nerve injury induces upregulation of the \(\alpha_2\delta\) subunit that is correlated with allodynic pain behavior. The \(\alpha_2\delta\) subunit expressed in the dorsal root ganglion, throughout the brain and spinal cord. Pregabalin is noted to block the \(\alpha_2\delta\) subunit sensitive voltage gated calcium channel, it has been reported to ameliorate neuropathic pain in animal model as well as human beings (Park et al., 2010). Gabapentin reverses allodynic behavior in rats with neuropathic pain and suppresses peripheral ectopic afferent discharge at injured nerve sites (Boroujerdi et al., 2011). Another anti-convulsant i.e., levetiracetam has been shown reduce the neuropathic pain in experimental models of pain as well as human beings via alteration of calcium channel function (Markman and Dworkin, 2006). Leconotide and ziconotide, derived from the venom of Conus magus, blocks N-type voltage sensitive calcium channel. The administration of leconotide and ziconotide has been documented to reduce the development of neuropathic pain in humans as well as experimental animals (Michiels, et al., 2011). Further, the novel selective and potent inhibitors of T-type calcium channel i.e., 4-piperidinecarboxylate and 4-piperidinecyanide have been reported to possess ameliorative effect in SNL-induced mechanical allodynia in rat (Woo et al., 2011). Moreover, the selective T-type calcium channel blocker i.e., 3,5-dichloro-N-[1-(2,2-dimethyl-tetrahydro-pyran-4-ylmethyl)-4-fluoro-piperidin-4-ylmethyl]-benzamide (TTA-P2) has also been shown to possess the attenuating effect on thermal hyperalgesia in diabetic rats (Choe et al., 2011).

3.II.C.2. Sodium Channel Blockers

Alterations in the level of expression, cellular localization, and distribution of Na\(^+\) channels are strongly associated with neuropathic pain (Wang et al., 2011). Fluctuation in the total levels of Na\(^+\) channel expression and the relative expression of each of the different channel subtypes contributes to hyper-excitability. The empiric analgesic efficacy of local anesthetics in clinical practice has supported this line of investigation. It is generally accepted that an increase in Na\(^+\) channel density lowers the nociceptive thresholds in injured neurons. These neurons have a heightened tendency toward action potential initiation and propagation.
Ion channel modulators preferentially inhibit abnormal excessive activity at ectopic foci with increased Na$^+$ channel density (Baron et al., 2006). An example of such activity has been demonstrated in the decreased spontaneous activity in experimental neuromas produced by carbamazepine (Markman and Dworkin, 2006). Blockade of the Na$^+$ channel preferentially impedes the upstroke where action potential initiation is most frequent. Spontaneous ectopic discharges are suppressed at much lower drug concentrations, thereby allowing normal impulse generation and propagation to continue. As a consequence Na$^+$ channel modulators possess a relatively large therapeutic window. Because ectopic firing is especially sensitive to Na$^+$ channel blockade, fatal toxicity due to failure of normal nerve conduction does not occur at drug concentrations that provide pain relief (Devor, 2006).

Clinical and experimental data indicates that changes in the expression of voltage-gated sodium channels in the dorsal horn play a key role in the pathogenesis of neuropathic pain and that drugs that antagonise these channels are potentially therapeutic (Amir et al., 2006). The available sodium-channel blockers are not selective and also act on neural and cardiovascular sodium channels, therefore adverse effects limit their use (Woolf and Mannion, 1999). Sodium-channel blockers used in human neuropathic pain include local anaesthetics, such as lidocaine and mexiletine (Kalso, 2005). The therapeutic dose of lidocaine for pain control is far below that which blocks nerves impulse propagation or affects cardiovascular functions, but its applicability is limited because it cannot be administered orally (Meurs et al., 2002). Although mexiletine is effective orally but an effective pain control dose is difficult to achieve due to its adverse effects (Kalso, 2005).

3.II.C.3. Potassium Channel Modulators
3.II.C.3.a. Potassium Channel Openers

The sensory symptoms have been noted to be produced by alteration of nerve impulses and development of ectopic axonal proteins with a redistribution of K$^+$ and Na$^+$ channels leading to the abnormal hyperexcitation (Roza and Lopez-Garcia, 2008). Retigabine acts as a potent opener of all K$^+$ channel alpha-subunits that possess two P-domains (KCNQ) subunits expressed in neurons and possess a good specificity when used at low concentrations. Retigabine has been noted to produce the beneficial effects on neuropathic pain by inducing spike frequency adaptation and stabilizing the resting membrane potential nervous system
Concomitantly, XE-991, a specific KCNQ/M-current blocker has been shown to reverse retigabine effects in a variety of neurons thus reinforcing that retigabine effects are mediated by functional KCNQ/M-currents (Xu et al., 2010). Hyperpolarisation of neuronal cell membrane can theoretically reduce excitatory neurotransmission. A number of compounds including the anti-inflammatory drugs like diclofenac, meclofenamic acid, and flupirtine possess this action (Chong and Brandner, 2006). Retigabine, a K(V)7.2/7.3 potassium voltage gated channel opener that increases the “M” current has been tested in humans after it is shown to be effective in animal models of neuropathic pain (Roza and Lopez-Garcia, 2008).

3.II.C.3.b. K2P Channels Modulators

Two pore domain potassium (K2P) channels are encoded and leak the K currents in the regulation of the resting membrane potential and excitability of nervous system. The fifteen members of the K2P channel family are divided into 6 subfamilies on the basis of their structural and functional properties; the families are TREK, TASK, TWIK, THIK, TRESK and TALK subfamilies (Alexander et al., 2009). The K2P channel activation is regulated by the variety of pharmacological and physiological mediators and neurotransmitters (Lodge and Li, 2008). The potential importance of K2P channels has been documented to be involved in the various therapeutic conditions such as neuroprotection, depression, anesthesia and epilepsy. The involvement of K2P channel activation has also been suggested in the pathogenesis of neuropathic pain (Mathie et al., 2010). TRESK (2-pore domain K+ channel, TRESK [TWIK (tandem-pore-domain weakly inward rectifying potassium channels) related spinal cord K+ channel] is specifically located in the spinal cord in humans and in the dorsal root ganglion (DRG) in mice (Kang and Kim, 2006). The selective activation of TREK-1 channel plays a key role in the polymodal pain perception. Studies also indicated that, TREKs and TRESK have the modulatory actions in the nociceptive pain sensation (Bayliss and Barrett, 2008). Thus, the diversity and physiological and pharmacological importance of K2P channels suggest that the development of selective compounds to target these channels may serve as good therapeutic agent for the management of neuropathic pain.

3.II.C.4. Transient Receptor Potential (TRP) Channel Modulators
3.II.C.4.a. Transient Receptor Potential Vanilloid (TRPV) Antagonists

On the basis of amino acid sequence homology, the transient receptor potential (TRP) superfamily can be divided into seven subfamilies: the TRPC (‘Canonical’) family; the TRPM (‘Melastatin’) family; the TRPV (‘Vanilloid’) family; the TRPP (‘Polycystin’) family; the TRPML (‘Mucolipin’) family; the TRPA (‘Ankyrin’) family; and the TRPN (‘NOMPC’) family. The TRPV subfamily contains six mammalian receptors (TRPV1–TRPV6), in addition to two receptors in non-mammals (Nilius et al., 2007). It should be noted that only TRPV1 from the TRPV subfamily is activated by vanilloids, such as capsaicin, hence the ‘Vanilloid’ subtype term. From the TRPV subfamily, TRPV1–TRPV4 is heat-activated receptors that are non-selective for cations, including Ca$^{2+}$. TRPV1 expression on sensory nerves (in particular C and A-δ fibres) is intrinsically associated with neurogenic inflammation (Kanai et al., 2005). Some endogenous agonists of TRPV1 have been shown to possess efficacy in animal models of pain, such as capsaicin-induced eye-wiping, capsaicin and Complete Freund's Adjuvant (CFA) induced hyperalgesia, and in neuropathic pain models including partial sciatic nerve injury and chronic constriction injury (Kanai et al., 2005). Further, specific TRPV1 antagonist i.e., N-(4-tertiarybutylphenyl)-4-(3-cholorphyridin-2-yl)tetrahydropryazine-1(2H)-carbox-amide (BCTC) administered intrathecally significantly attenuated mechanical allodynia in animals with CCI-induced neuropathic pain (Kanai et al., 2005). All these studies suggest that TRPV1 is an essential receptor in peripheral neuropathic pain production mechanisms (Nilius et al., 2007) and it can be good target to manage neuropathic pain.

3.II.C.4.b. TRPM$_8$ Cold Receptor Modulators

Since Hippocrates and Galen, sporadic reports have described the use of cooling to produce analgesia. Clinical trials show beneficial effects of cooling on chronic back pain, dental pain, postoperative pain, and muscle injuries (Caspani et al., 2009). Preparations containing menthol, which produce a cool sensation, are used topically to relieve neuralgia in traditional Chinese and European medicine (Albin et al., 2008). Mint oil has been reported to alleviate thermally elicited pain and postherpetic neuralgia and oral menthol can cause short-term analgesia (Sousa et al., 2009). Furthermore, in mice, oral or intracerebroventricular application of menthol is noted to decrease nociceptive responses to the hot-plate test and
acetic-acid writhing test (Galeotti et al., 2002). The recent isolation of the transient receptor potential cation channels present in primary sensory neurons has revolutionized the understanding of cutaneous temperature detection. The best-characterized example is the capsaicin- and heat-sensitive TRPV1 receptor (considered as a ‘pathological’ receptor) (Okun et al., 2011), and although much less is known about cool-sensitive TRPs, they are the target of intensive research. TRPM8 is activated at innocuous cool temperatures (with 50% activation around 18°C–19°C and by menthol and icious, which act as selective activators of the channel (Albin et al., 2008; Sousa et al., 2009). The TRPM8 channel is expressed by a subpopulation of sensory neurons in dorsal root ganglia (DRG) and trigeminal ganglia, where responses to cooling correlate well with mRNA expression and menthol sensitivity (Babes et al., 2004). TRPM8 expression has been shown to be increased in a subset of sensory neurons after nerve injury. The analgesic effect of TRPM8 activation is centrally mediated and relies on Group II/III metabotropic glutamate receptors (mGluRs), but not opioid receptors. Group II/III mGluRs can respond to glutamate released from TRPM8-containing afferents to exert an inhibitory gate control over nociceptive inputs. The TRPA1 channel is also expressed in DRG and trigeminal ganglia and is reportedly activated by cooling temperatures beginning 5°C–6°C lower than that for TRPM8 and by noxious chemicals such as cinnamaldehyde and mustard oil (Albin et al., 2008).

Moreover, reports have demonstrated marked analgesic effects of peripherally or centrally applied TRPM8 activators (such as icious or menthol), or mild cooling of the skin, in a model of neuropathic pain (McCoy et al., 2011). Intrathecal application of TRPM8 activators near the central terminals would also produce analgesia. Intrathecal injection of icious (10 nmol) produced robust reversal of CCI-induced behavioral-reflex sensitization in thermal and mechanical tests. The effects of TRPM8 activators, the TRPA1 activator, cinnamaldehyde (75 nmol injected intrathecally), significantly increased reflex responsiveness in thermal and mechanical tests and was effective contralateral as well as ipsilateral to nerve injury (Proudfoot et al., 2006). These findings show that both peripheral and central activation of TRPM8 can produce an analgesic effect that specifically reverses the sensitization of behavioral reflexes elicited by peripheral nerve injury. TRPM8 activators and downstream central mediators of TRPM8 action, such as Group II/III mGluRs, would be a novel target for the management of neuropathic pain.
3.II.D. Ion Exchanger Modulators

3.II.D.1. Sodium Calcium and Sodium Hydrogen Exchanger (NCE / NHE) Modulators

Na\(^+\)/Ca\(^{2+}\) exchanger (NCX) is a bi-directional membrane ion transporter and it consists of about 930 amino acids having nine trans-membrane domains (TMD). It is expressed ubiquitously in the plasma membrane of cells and plays an important role in regulating intracellular Ca\(^{2+}\) ion concentration. In the nervous system, NCX is primarily involved in extruding excess intracellular calcium. In pathological condition, it is operated in reverse direction to cause accumulation of cytosolic calcium levels (Muthuraman et al., 2008). The reverse mode of activation of NCX exchanger has been involved in the vincristine, tibial and sural nerve transection and chronic constriction injury of sciatic nerve induced neuropathic pain disorders (Muthuraman et al., 2008a; Kaur et al., 2010).

Sodium hydrogen (Na\(^+\)/H\(^+\)) exchanger is a family of membrane proteins that regulate ions fluxes across membrane. Na\(^+\)/H\(^+\) exchanger (NHE) activation induced intracellular alkalization has been demonstrated to increase the NCX activity because the NCX activity depends on intracellular pH (Muthuraman et al., 2008a). Na\(^+\)/H\(^+\) exchanger is involved in variety of physiological and pathological events that include regulation of intracellular pH, cellular mobility, intra and extra cellular calcium regulation, and it is also reported to cause the development of chronic constriction injury of sciatic nerve induced painful neuropathy (Muthuraman et al., 2008).

Activation of Na\(^+\)/Ca\(^{2+}\) and Na\(^+\)/H\(^+\) exchanger induced calcium accumulation have been implicated to promote neuronal and tissue injury (Kaur et al., 2010). Calcium accumulation has been well documented to play an important role in post-traumatic (Mirzayan et al., 2008), axotomy (Muthuraman et al., 2008), anti HIV drugs (Lokesh et al., 2006), vincristine, and chronic constriction injury induced painful neuropathy (Muthuraman and Singh, 2011; Muthuraman et al., 2011). Amiloride dual inhibitor of Na\(^+\)/Ca\(^{2+}\) and Na\(^+\)/H\(^+\) exchanger has been demonstrated to provide beneficial effect in neuropathic pain (Muthuraman et al., 2008). It has been reported that decrease in the cellular Ca\(^{2+}\) ions accumulations, due to inhibition of Na\(^+\)/Ca\(^{2+}\) and Na\(^+\)/H\(^+\) exchanger, is responsible for antinociceptive effects of amiloride. Pralidoxime an inhibitor of Na\(^+\)/Ca\(^{2+}\) exchanger has been reported to cause attenuation of vincristine, CCI of sciatic nerve and TST induced rise in
neuronal Ca\(^{2+}\) ions and development of neuropathic pain perception (Muthuraman et al., 2008; Kaur et al., 2010).

3.II.E. Ion / Molecule Transport Modulators

3.II.E.1. Sodium Potassium and Chloride Cotransporter-1 (NKCC-1) Modulators

Sodium potassium and chloride cotransporter-1 (NKCC-1) is noted to be present in the spinal cord and nervous system. In the primary sensory neurons, direct inward movement of intracellular Cl\(^-\) occurs through Na\(^+\)-K\(^+\)-Cl\(^-\) cotransporter 1 (NKCC1), whereas direct outward movement of intracellular Cl\(^-\) occurs through K\(^+\)–Cl\(^-\) cotransporter 2 (KCC2). Some studies have shown that increase in NKCC-1 occurs in peripheral nerve injury or inflammation (Wei et al., 2010) and this induces the down-regulation of KCC2 in the spinal dorsal horn. Further, it has been reported that inhibition of GABA\(_A\) receptor leads to neuronal firing, excitation and activation of pain-relay system in neuron along with rise in phosphorylation, membrane mobilization and expression of NKCC1 protein in the spinal cord (Cramer et al., 2008). These processes lead to increase in intracellular chloride concentration, excessive depolarization of primary afferent nerve fibers and generation of abnormal neuronal action potential. Bumetanide is a blocker of NKCC-1; it has been reported to possess potential ameliorative effect in painful neuropathy and neuroinflammation (Wei et al., 2010). Therefore, modulators of sodium potassium and chloride cotransporter-1 may also serve as novel pharmacological therapeutic targets for management of neuropathic pain.

3.II.E.2. Glycine Transporter Inhibitors

Neuronal sensitivity involves the activation of stimulatory spinal neurotransmission, recent findings emphasize that a reduction in the strength of \(\gamma\)-amino-butyric acid (GABA)\(_A\) receptor- and glycine receptor (GlyR)-mediated synaptic inhibition; i.e., disinhibition of inhibitory neurotransmission within the dorsal horn, is implicated in the generation of inflammatory and neuropathic pain. Such disinhibition includes reduced inhibitory transmitter synthesis and/or release, loss of inhibitory interneurons, and altered descending inhibitory modulation from the brain (Miraucourt et al., 2009). Glycinergic inhibition by an inhibitor of glycine release or blockers of GlyR in the dorsal horn can elicit tactile allodynia (Esmaeili and Zaker, 2011). In contrast, agonists of glycine and GABA\(_A\) receptors have anti-allodynic
effects (Hinckley et al., 2005). The stimulation of the α7 and α4α2 nicotinic acetylcholine receptor subtypes in the spinal cord reduced tactile allodynia by stimulating spinal glycine inhibitory neurotransmission in a tibial nerve transected neuropathic pain model in rats (Eaton et al., 2007). The extracellular concentrations of glycine at glycineergic nerve terminals are regulated by the Na\(^+\)/Cl\(^-\) dependent glycine transporters (GlyT) GlyT\(_1\) and GlyT\(_2\). Peripheral nerve injury leads to reduced inhibitory control subsequently opening the gates to pathological neuropathic pain signaling in the superficial dorsal horn of the spinal cord (Hinckley et al., 2005). Selective GlyTs inhibitors i.e., sarcosine and N-[3-(4′-fluorophenyl)-3-(4′-phenylphenoxy)propyl]sarcosine (NFPP) have been noted to produce antinociceptive effects against thermal hyperalgesia in a sciatic nerve injury model (Tanabe et al., 2008), in the complete Freund’s adjuvant (CFA)-induced chronic inflammation model, in formalin-induced pain model and in acetic acid induced writhing syndrome (Dohi et al., 2009).

3.II. F. Receptor Modulators
3.II. F.1. Histamine Receptor Modulators

Histamine is a established chemical mediator of inflammation, anaphylaxis, various allergic and painful conditions. Physiologically, peripheral injection of histamine into the skin causes excitation of polymodal nociceptors producing an itch sensation (de Oliveira et al., 2011). It acts at four known types of histamine receptors (H\(_1\)-H\(_4\)) and has been widely implicated in the development of nociception and neuropathic pain. Blocking of histamine H\(_1\) and H\(_2\) receptors has been well established to reduce neuropathic pain after peripheral and central neuronal injury (Tamaddonfard et al., 2008; Hsieh et al., 2010). Further, some limited studies have also reported the role of histamine H\(_3\) and H\(_4\) receptors in neuropathic pain (Hough and Rice, 2010; Hsieh et al., 2010). The therapeutic action on histamine associated neuropathic pain occurs by two ways i.e., (1) reduction of histamine release and (2) blocking of histamine receptors. In the pathological situation, histamine is released from the inflammed and injured sites by the activation of various immune and immune like cells. Mast cell plays major role in the abundant release of histamine causing allergy and nociceptive pain sensation. The mast cell stabilizer like sodium cromoglycate which inhibit histamine release have been shown to inhibit the development of neuropathic pain (De Filippis et al., 2011). Histamine-1 (H\(_1\)) receptors mRNA are predominantly expressed and localized in primary...
sensory neurons and superficial dorsal horn. Histamine primarily binds to H1 receptors of the nervous system and it also acts as a neurotransmitter to induce the nociceptive pain sensation via histaminergic nervous system (Hough and Rice, 2010). H1 receptor antagonists such as chlorpheniramine, pyrilamine, dexchlorpheniramine, diphenhydramine, promethazine, and cetirizine have been documented to exert potent anti-nociceptive actions in animals and humans (Ashmawi et al., 2009). Few studies report that H2 receptors also control pain perception. The H2 blocker i.e., ranitidine has been reported to reduce the acute trigeminal nerve injury and partial sciatic nerve ligation-induced neuropathic pain in rats (Tamaddonfard et al., 2008). Another H2-receptor antagonist i.e., famotidine has also been reported to reduce the formalin-induced nociceptive pain sensation in rats (Mojtahedin et al., 2008). Further, the non-selective H2 receptor antagonists i.e., zolantidine, cimetidine have also been documented to reduce the tail-flick latency in rats (Hasanein, 2011). The mechanism of H2 receptors mediated modulation of pain perception has been documented through elevation of endogenous opioid (Hasanein, 2011).

The H3 receptors are located on peripheral and spinal terminals of deep dermal fibers and activation of H3 receptors has also been reported to attenuate nociceptive pain sensation. In situ hybridization studies have also found that the H3 receptor density is highest in the brain, dorsal root ganglia, spinal cord and selected peripheral tissues. In contrast, the activation of H3 receptors is known to reduce the release of inflammatory peptides, thereby, reducing pain and inflammation (Cannon et al., 2007). The inhibition of the activity of H3 receptor has been expected to modulate pain transmission. In fact, oral administration of the H3 agonist prodrug BP 2-94 reduces nociceptive pain responses. Further, the H3 agonist immepip has been shown to attenuate mechanical hyperalgesia in rats (Hough and Rice, 2010). The presynaptic localization of H3 receptors on sensory neuronal fibers along with H3-mediated inhibition of transmitter release strongly suggest that immepip produces anti-nociception by reducing sensory fiber transmitter release at spinal presynaptic sites (Cannon et al., 2007). Administration of H3/H4 receptor inverse agonist i.e., thioperamide; specific H4 receptor antagonist i.e., JNJ 7777120, and H4 receptor agonist VUF 8430 have been demonstrated to attenuate mechanical hyperalgesia in neuropathic pain models (Smith et al., 2007; Huang et al., 2007).
3.II.F.2. Serotonin (5-hydroxytryptamine) Receptor-1A (5-HT\textsubscript{1A}) Modulators

Serotonin (5-HT) is involved in the transmission of nociception in the central nervous system and inhibits nociceptive responses, wind-up and after-discharges in spinal neurons through an action on 5-HT\textsubscript{1A} receptors. Selective, high-efficacy 5-HT\textsubscript{1A} receptor agonist, F13640 has been reported to produce long-term analgesia in rodent models of peripheral neuropathic pain and it also has a curative-like action on allodynia in rats with spinal cord injury (Guenther et al., 2009). It appears to induce two neuroadaptive phenomena: firstly, activation of 5-HT\textsubscript{1A} receptors which cooperate with nociceptive stimulation, but paradoxically cause analgesia, and secondly, inverse tolerance, so that the resulting analgesic effect increases rather than diminishes. Many anti-depressants affect serotonin concentration in the CNS but, surprisingly, selective serotonin reuptake inhibitors such as fluoxetine are ineffective in neuropathic pain models. In contrast, antidepressants acting on the noradrenergic system (for example milnacipran and duloxetine) or both the noradrenergic and serotonergic systems (for example amitriptyline) are effective (Lee and Chen, 2010). The analgesic action of anti-depressants is more likely to be a reflection of sodium channel blockade, since fluoxetine for example, produces a substantially slower blockade than amitriptyline (Dick et al., 2007). Serotoninergic receptor-1A (5-HT\textsubscript{1A}) can be a good therapeutic target for the management of neuropathic pain.

3.II.F.3. Dopamine Receptor (D\textsubscript{1}R and D\textsubscript{2}R) Modulators

Dopamine has been demonstrated to play a major role in pain signal processing in multiple levels of the central nervous system including the spinal cord, periaqueductal gray (PAG), thalamus, basal ganglia, insular cortex, and cingulate cortex. The decreased levels of dopamine have been associated with painful symptoms that frequently occur with Parkinson's disease. Abnormalities in dopaminergic neurotransmission have also been demonstrated in painful clinical conditions (Wood et al., 2007). In general, the analgesic capacity of dopamine occurs as a result of dopamine D\textsubscript{2} receptor activation in the PAG and dopamine D\textsubscript{1} receptor activation which attenuates pain via activation of neurons involved in descending inhibition. In addition, D\textsubscript{1} receptor activation in the insular cortex appears to attenuate subsequent pain-related behavior. The insular cortex receives somatosensory afferent input and has been related to nociceptive input. D\textsubscript{2}R agonist and D\textsubscript{1}R antagonist are observed to act on the insular
cortex and diminish the nerve transection (axotomy)-induced neuropathic pain (Coffeen et al., 2010).

The chronic administration of D₁ and D₂ receptor agonist i.e., dopamine has been reported to modulate the chronic constriction injury (CCI) and the spared nerve injury (SNI)-induced neuropathic pain in rats via decreasing the level of BDNF and an increasing the levels of IL-1β, IL-6, NGF and GDNF in different brain region i.e., cingulum, striatum, and hippocampus (Al-Amin et al., 2011). The administration of levodopa has been shown to produce anti-nociceptive effect in a rat model of painful mononeuropathy. Moreover, the systemic administration of levodopa produced a decrease in tactile and cold allodynia. Further, direct intrathecal (i.t.) administration of levodopa at lumbar regions produces a similar anti-allodynic effect. The involvement of the spinal dopaminergic system and anti-nociceptive effect on neuropathic pain has been confirmed by D₂-type receptor antagonist i.e., sulpiride (Cobacho et al., 2010). The contribution of rostral agranular insular cortex and dorsolateral striatum have also been documented in the modulation of neuropathic pain processing by administration of dopamine D₁R antagonist i.e., SCH-23390, D₁R agonist i.e., SKF-38393, D₂R agonist i.e., TNPA, and a dopamine D₂R antagonist i.e., spiperone. It has been suggested that dopamine receptors within the RAIC have differential role whereby activation of D₂R and blockade of D₁R produce anti-noception (Coffeen et al., 2008).

3.II.F.4. Alpha-1 (α1) and Alpha-2 (α2) Adrenergic Receptor Modulators

Sympathetic nerve block by phentolamine (α-adrenoreceptor antagonist) administration has long been used for diagnosis and treatment of neuropathic pain patients (Kim et al., 2005). In experimental animal models, peripheral nerve injury results in the sprouting of sympathetic fibers into dorsal root ganglion and neuropathic symptoms can be alleviated by surgical sympathectomy or sympathetic nerve block such as with phentolamine administration (Daniel et al., 2009), although few studies reported the opposite (Huang et al., 2011; Ilfeld, 2011). Accordingly, numerous studies have attempted to elucidate the effects of specific α-adrenoreceptor subtype antagonists on neuropathic pain. However, the administration of α₁ or α₂-adrenoreceptor antagonists has produced inconsistent results (Tanabe et al., 2005). Information is thus unclear regarding the roles of α₁- and α₂-adrenoreceptor and the effects of their antagonists in neuropathic pain.
The $\alpha_1$- and/or $\alpha_2$-adrenoreceptor are suggested to be responsible for the adrenergic mediated pain sensation of neuropathic rats. Prazosin ($\alpha_1$-adrenoreceptor antagonist) or yohimbine ($\alpha_2$-adrenoreceptor antagonist) has been reported to possess the beneficial effect on rat tail model of neuropathic pain (Kim et al., 2005). Some studies have documented dual contribution of $\alpha_1$- and $\alpha_2$-adrenoreceptor antagonist in ameliorating neuropathic pain. Nam et al. reported that yohimbine significantly relieves hyperalgesia while phenylephrine ($\alpha_1$-adrenoreceptor agonist) exacerbates it, but prazosin and clonidine ($\alpha_2$-adrenoreceptor agonist) has no significant effect (Nam et al., 2000). The alpha-2 agonist clonidine has been shown to produce analgesia at the spinal level through stimulation of adrenergic inter-neurons in the spinal cord (Park et al., 2010). However, it is administered neuraxially for neuropathic pain and results of some clinical trials in people have been disappointing. Moreover, strain difference may be an important factor in determining the degree of adrenergic dependency of pain behaviors as well as the subtype of $\alpha$-adrenoreceptor mediating the effect (Daniel et al., 2009). Further, some studies have also reported that, $\alpha_2$-adrenoreceptor agonists i.e., ST-91 and Tizanidine possess anti-nociceptive effects in the management of painful neuropathy (Fairbanks et al., 2009).

3.II.F.5. Beta-2 ($\beta_2$) Adrenergic Receptor Modulators

The $\beta_2$-adrenergic receptors are expressed within the dorsal horn of the spinal cord which is the first integrative center for nociceptive information. The $\beta_2$-adrenergic receptors dependent nociceptive mechanisms might be a secondary recruitment of a delta-opioid receptors tone which is responsible for the final anti-allodynic action (Benbouzid et al., 2008; Perret and Luo, 2009; Yalcin et al., 2009a). Various anti-depressant drugs have been studied in the management of neuropathic pain and it has been suggested that adrenoceptors may play a critical role in their anti-allodynic actions (Benbouzid et al., 2008). Further, it is demonstrated that neither $\alpha_2$-adrenoceptors, $\beta_1$-adrenoceptors, and nor $\beta_3$-adrenoceptors are important for anti-depressant drug action against neuropathic pain (Alexander et al., 2009; Yalcin et al., 2009a). On the contrary, the absence or the blockade of $\beta_2$-adrenoceptors totally suppressed the effect of chronic nortriptyline, desipramine, venlafaxine or reboxetine treatments on mechanical allodynia (Yalcin et al., 2009a). Hence stimulation of $\beta_2$-adrenoceptors is necessary for anti-depressant drug action against neuropathic pain (Yalcin et
Further, the chronic treatment (but not the acute treatment) with non-selective β-adrenoceptor agonists such as bambuterol and isoprenaline along with different β2-adrenoceptor agonists such as fenoterol, salbutamol, salmeterol, ritodrine and terbutaline have been documented to alleviate neuropathic pain in mice (Choucair-Jaafar et al., 2009). Anti-allodynic action of β-adrenoceptor agonists are reversed by intraperitoneal or intrathecal, but not intracerebroventricular or intraplantar, co-treatment with the β2-adrenoceptor antagonist ICI118551 in murine model of peripheral neuropathy (Choucair-Jaafar et al., 2009). Adrenaline is known to induce mechanical hyperalgesia and sensitize dorsal root ganglia by acting on β-adrenoceptors (Choucair-Jaafar et al., 2009), and β2-adrenoceptor antagonist decrease allodynia or hyperalgesia in inflammatory pain (Nackley-Neely et al., 2007). The clinical use of TCAs is limited due to various side effects (Choucair-Jaafar et al., 2009), and potentially, β2-adrenoceptor agonists could offer a therapeutic alternative to TCAs for neuropathic pain management and could serve as better therapeutic agents for chronic pain therapy.

3.II.F.6. Purinergic Receptor Modulators

In the spinal cord, adenosine A1 receptor activation produces anti-noceptive properties in acute nociceptive, inflammatory and neuropathic pain tests. Recent studies showed that increase in extracellular adenosine levels and subsequent receptor activation are involved in the peripheral anti-nociceptive effect of amitriptyline in nerve injury-induced neuropatic pain in rats, since co-administration of modest doses of caffeine reduces the action of acutely and chronically administered amitriptyline (Sawynok et al., 2008). Clinical studies in healthy volunteers showed that intrathecal adenosine administration attenuated several types of experimental pain without causing significant side effects (Hayashida et al., 2005). Accordingly, allosteric modulation of adenosine A1 receptors reduces allodynia, and, more interesting, the allosteric modulator T62 (2-amino-3-(4-chlorobenzoyl)-5,6,7,8-tetrahydrobenzothiophen) was effective not only after intrathecal injection but also after systemic administration (Obata et al., 2004).

There is abundant evidence that extracellular ATP and microglia have an important role in neuropathic pain. ATP is released from damaged cells as a result of ischemia or inflammation and serves as a cell-to-cell mediator through cell surface purinergic P2
receptors, which are widely distributed throughout the nervous system, including microglia. P2 receptors are divided into 2 subtypes: P2X and P2Y (Hayes et al., 2008). P2X receptors (P2X1–P2X7) are coupled to nonselective cation channels, allowing the influx of Na\(^+\) and Ca\(^{2+}\) (Kobayashi et al., 2011), whereas P2Y receptors (P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, P2Y13, and P2Y14) are G-protein coupled, and their activation leads to inositol lipid hydrolysis, intracellular Ca\(^{2+}\) mobilization, or modulation of adenylate cyclase activation (Inoue, 2006). P2X4 receptor subtype in the activated spinal microglia is required for the expression of neuropathic pain after nerve injury (Casas-Pruneda et al., 2009). The expression of P2X4 receptor, a subtype of ATP receptors, is enhanced in spinal microglia after peripheral nerve injury, and blocking pharmacologically and suppressing molecularly P2X4 receptors produce a reduction of the neuropathic pain. ATP is able to activate MAPK, leading to the release of bioactive substances, including cytokines, from microglia (Inoue, 2006). Thus, diffusible factors released from activated microglia by the stimulation of purinergic receptors may have an important role in the development of neuropathic pain (He et al., 2012; Inoue, 2006). Downregulation of P2X3 expression using antisense oligonucleotides or siRNA in rats and disruption of the P2X3 gene in mice have also strongly supported a pronociceptive role for this receptor, particularly after inflammation or injury (Dorn et al., 2004). Increased expression of P2X3R in the sensory nervous system play a pivotal role in developing and maintaining heat hyperalgesia induced by partial nerve injury, and thus P2X3R antagonist (PPADS, pyridoxal-phosphate-6-azophenyl-2',4'-disulfonic acid) aliviate the symptoms of neuropathic pain (Shinoda et al., 2007).

3.II.F.7. Excitatory Amino Acid (EAA) Receptor Modulators

It has been hypothesized that EAAs (e.g., glutamate and aspartate) may play a role in the development and maintenance of neuropathic pain. Since central sensitization is hypothesized to be associated with N-methyl D-aspartate (NMDA) and/or non-NMDA receptor activation, it is reasonable to evaluate both NMDA and non-NMDA antagonists as possible agents for treatment of neuropathic pain. NMDA receptor antagonists, including 5-Methyl-10,11-dihydro-5H-dibenzo[a,d]cycohepten-5,10-imine maleate (MK-801), dextrophan and ketamine are considered potential agents for therapeutic use in the treatment of neuropathic pain due to their antinociceptive effects following nerve injury in human and
animal studies (Yoshimura and Yonehara, 2006). However, studies assessing their potential usefulness have also found deleterious adverse effects including hyperlocomotion and motor impairment (Satow et al., 2008).

3.II.F.7.a. Glutamate Receptor Modulator

Despite the important role of glutamate in spinal nociceptive processing, there have not been many studies exploring the role of metabotropic glutamate receptors (mGluRs) in nociceptive transmission (Chen and Pan, 2005). Among group I mGluRs, mGluR5 seems to be involved in the modulation of nociceptive information, as this receptor has been found in nociceptive pathways (e.g., dorsal root ganglia (DRG) and spinal dorsal horn neurons) (Satow et al., 2008). Additionally, some results have shown that antagonists of mGluR5, like 2-methyl-6-phenylethyl-pyrididine (MPEP), inhibit inflammatory and neuropathic pain in rats (Zhu et al., 2004) and in mice (Varty et al., 2005). In contrast to group I mGluRs, the involvement of groups II and III mGluRs in nociceptive processes is most likely due to their established ability to decrease glutamate release from the central nervous system (Satow et al., 2008). Also, their localization in nociceptive pathways may suggest their involvement in pain; both mGluR2/3 and mGluR7 have been detected in the spinal dorsal horn and DRG. Agonists of mGluR2/3 have been shown to produce antinociceptive effects in inflammation and neuropathy (Zhang et al., 2009). In consequence of mGluR5 blockade by the antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine (MTEP), the persistent activation of NMDARs in neuropathic pain could be decreased via PKC-dependent mechanism and morphine action could be potentiated (Varty et al., 2005; Sluka and Audette, 2006). The development of selective mGluR ligands has provided important tools for further investigation of the role of mGluRs in the modulation of chronic pain processing (Zhu et al., 2004). Osikowicz et al. have demonstrated that MPEP (mGluR5 antagonist), LY379268 (mGluR2/3 agonist) and AMN082 (mGluR7 agonist) decrease the CCI-induced neuropathic pain symptoms in mice (Osikowicz et al., 2008).

3.II.F.7.b. AMPA Receptor Antagonist

The therapeutic potential of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor blockers in chronic sensitised pain states has been largely overlooked,
because AMPA receptors contribute to the acute spinal processing of both nociceptive and non-nociceptive inputs in the spinal cord (Garry and Fleetwood-Walker, 2004). These findings are consistent with reports of a role for both NMDA and AMPA receptors in neuropathic hyperalgesia. A number of proteins that interact with the intracellular C-terminal of postsynaptic AMPA receptor GluR1-4 subunits have been identified (Sluka and Audette, 2006; Wang et al., 2010).

AMPA receptors associated GluR1 levels have also been reported to increase in neuropathic pain. Activation of AMPA receptor underlies pain and enhances spinal activity after thermal stimulation and/or incision injury (Pogatzki et al., 2003). Midazolam has been noted to regulate the spinal AMPA receptor expression and functional recovery from nerve injury-induced neuropathic pain behavioural changes in rats (Jonas et al., 1998). Moreover, AMPA receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione disodium salt (CNQX) has also been documented to ameliorate substance-P induced thermal hyperalgesia (Nakayama et al., 2010).

3.II.F.7.c. Kainate Receptor Antagonist

Kainate receptors have been suggested to inhibit nociceptive transmission. These receptors are located on the terminals of primary afferent C-fibers and on cell bodies in the dorsal root ganglia. It has been demonstrated that kainate or L-glutamate depolarizes and subsequently desensitizes C-fibers by acting at the kainate receptor and kainate also depresses electrically evoked volleys in C-fibers (Rodríguez-Moreno and Sihra, 2011). SYM-2081 (4-methylglutamic acid) a selective kainite receptor antagonist has been reported to produce long duration desensitization of nociceptors suggesting that kainate receptor antagonists can inhibit nociceptive transmission (Turner et al., 2003). SYM-2081 appears to suppress nociceptive transmission as evidenced by attenuation of the frequency and latency of responses to mechanical and thermal cold (-4°C) stimuli injury induced model of neuropathic pain (Ta et al., 2000).

3.II.F.8. Sigma (σ) Receptor Antagonists

Morphine and other μ, κ and δ-opioid receptor agonists are shown to be effective in acute thermal nociceptive tests. Few studies have documented about the use of sigma
receptors in neuropathic pain. Sigma receptors have been classified into two subtypes (σ1R and σ2R). From a functional point of view, the σ1R has been proposed to be a modulator of a variety of receptors and ion channels, acting as amplifiers in signal transduction cascades. At the endoplasmic reticulum the σ1R acts as a chaperone regulating the flow of Ca2+ via inositol 1,4,5-trisphosphate (IP3) receptors (Hayashi and Su, 2007). In addition, σ1R regulates inter-organellar Ca2+ signaling. Other relevant functions are to regulate components of plasma membrane-bound signal transduction such as phospholipase C and protein kinase C activities and, importantly, modulation of activity of neurotransmitter receptors and ion channels, including K+ channels, Ca2+ channels, N-methyl-D-aspartate (NMDA), dopamine and γ-aminobutyric acid (GABA) receptors (Martina et al., 2007). Systemic administration of haloperidol and haloperidol metabolites I and II (with an order of potency which correlated with their affinity for σ1Rs) have shown anti-nociception in mice (Cendan et al., 2005). Furthermore, intrathecal administrations of σ1R antagonist i.e., N-[2-(3,4-Dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino)ethylamine dihydrobromide (BD1047) is observed to reduce formalin and nerve injury-induced pain behaviours therefore, suggesting a role of sigma receptor in neuropathic pain (Roh et al., 2008). The administration of signal receptor antagonist i.e., 1'-benzyl-3-methoxy-3H-spiro[2]benzofuran-1,4'-piperidine (BMSBP) has been shown to possess the beneficial effect in capsaicin-induced antinociceptive action in human as well as in rat models (Wiese et al., 2009).

3.II.F.9. Opioid Receptor-like Receptor (ORL1) Agonists

ORL1 receptor is a member of the "family" of opioid receptors, it is structurally similar to that of opioid receptors but there is no similarity to pharmacological homology. Moreover, the non-selective opioid ligands that exhibit high affinity towards mu, kappa, and delta opioid receptors and have very low affinity for the ORL1 receptor therefore it is also called an "orphan opioid receptor". However, the endogenous opioid ligand such as dynorphins, enkephalins, endorphins, endomorphins and nociceptin have high affinity to binds with ORL1 receptor (Obara et al., 2005). Four major subtypes of opioid receptors have been identified i.e., OP1 delta (subunits: δ1, δ2), OP2 kappa (subunits: κ1, κ2, κ3), OP3 mu (subunits: μ1, μ2, μ3), and OP4 called nociceptin or delta receptor (opioid receptor-like receptor-1, ORL1). ORL1 receptors are distributed in different brain region i.e., cortex,
amygdale, hippocampus, septal nuclei, habenula, and hypothalamus, as well as in spinal cord (Obara et al., 2005).

The administration of nociceptin/orphanin FQ, an endogenous ligand for the orphan ORL₁ receptor, has been reported to attenuate the diabetic and mononeuritis induced mechanical hyperalgesia in rats. It is suggested that the ORL₁ receptor play a potential role in the management of neuropathic pain (Courteix et al., 2004). The administration of opioid receptor-like (ORL₁) receptor agonist i.e., Ro64-6198 has been reported to ameliorate experimental model of neuropathic pain in rat. The similar effect has been observed by administration of nociceptin/orphanin FQ (N/OFQ). Administration of selective antagonists of the ORL₁ receptor i.e., Phe₁Psin(CH₂-NH)Gly₂]NC(1-13)NH₂ (PhePsi) and [N-Phe₁]-NC(1-13)NH₂ (NPhe) attenuate Ro64-6198 induced anti-allodynic actions (Obara et al., 2005).

3.II.F.10. Endothelins Receptor (ETₐ and ETₐ) Modulators

Endothelins (ET) are small peptides isolated as a secretion product of endothelial cells and may contribute in the development of neuropathic pain. The endogenous ETs significantly contribute to pain and/or hyperalgesia of inflammation, immune, neuropathic, and neoplastic origins (Chichorro et al., 2006). There are three endothelial peptides i.e., ET-1, ET-2, and ET-3 that play important roles in diverse biologic processes largely through the control of vascular tone and are therefore receiving considerable attention as targets for anti-hypertensive and anti-tumor therapies. ET converting enzymes act on biologically inactive ET, converge it to active ligand, which then engages G protein coupled receptors (ETₐ and ETₐ) to initiate and differentially specify signal transduction cascades. ET axis has confirmed that ET signaling is critical for normal development of neural crest, heart and unmasked roles in pain pathways (Lee et al., 2003). Endothelins (ETs) contribute to the sensory changes seen in inflammatory, cancer, diabetic mellitus, L₅/L₆ spinal nerve ligation (SNL), Chronic constriction (C) of the infra-orbital nerve (ION) nerve injury induced peripheral and central neuropathic pain (Chichorro et al., 2006; Werner et al., 2010).

The administration of ET-1 has been observed to cause potential nociception; hyperalgesia and/or allodynia produced due to chemical, mechanical and thermal sensory stimuli in laboratory animals (Werner et al., 2010), and burning pruritus, deep muscular pain, mechanical tenderness and cold hyperalgesia in humans (Khodorova et al., 2009). Thus ET-1
mediated pain signaling is a complex integration of ET\textsubscript{A}-mediated activation of nociceptors on primary sensory neurons and ET\textsubscript{B}–mediated activation of central neurons signals. The ET\textsubscript{B} receptors mediated analgesic effects are negative regulation of pain signalling mechanism i.e., the activation of ET\textsubscript{B} receptors has been shown to release the peripheral endorphins from keratinocytes (Werner \textit{et al.}, 2010). Dorsal root ganglion small diameter neurons contain abundant ET\textsubscript{A} receptors (Chichorro \textit{et al.}, 2006). The administration of ET-1 at peripheral site and/or applied to sciatic nerve causes neuropathic pain with signal transmission from the periphery to the central nervous system via sensory fibers after ET\textsubscript{A} receptor activation. Further it also causes the activation of analgesic pathways via activation ET\textsubscript{B} receptor in some situations (Werner \textit{et al.}, 2010).

ET-1 induces hind paw flinch response and concomitant activation of sensory C and A\textdelta fibers in the sciatic nerve of the rat via ET\textsubscript{A} receptors. SNL has also been reported to induce the marked thermal stimulation via up-regulation of pronociceptive ET\textsubscript{A} and ET\textsubscript{B} receptor peripheral sensory nerve system (Werner \textit{et al.}, 2010). Moreover, mechanism of ET-1-induced heat hyperalgesia involves the activation of ET\textsubscript{A} receptors, PK\textsubscript{C} and TRPV1 activation (Kawamata \textit{et al.}, 2008). Selective ET\textsubscript{A} receptor antagonist (atrasentan) and selective ET\textsubscript{B} receptor antagonist (BQ-123 and BQ-788) have been reported to reduce endothelin-1-induced neuropathic pain (Werner \textit{et al.}, 2010). In addition, the elevation of ET\textsubscript{A} and ET\textsubscript{B} receptor protein levels in L\textsubscript{4}-L\textsubscript{6} spinal nerves from SNL rats has been observed. Further, the CCI of sciatic nerve in rats has also been reported to up-regulate both ET-1 and the ET\textsubscript{A} receptor proteins level at the site of injury along with changes in neuropathic pain behaviours. The intravenous (i.v.) administration of the nonselective ET receptor antagonists i.e., bosentan and selective ET\textsubscript{A} i.e., atrasentan but not selective ET\textsubscript{B} i.e., A-192621, has been documented to ameliorate diabetic peripheral neuropathy (Peters \textit{et al.}, 2004).

3.II.F.11. Kinin B\textsubscript{1} and B\textsubscript{2} Receptor Antagonists

Nerve injury is accompanied by a local inflammatory reaction in which nerve-associated cells and immune cells release several pronociceptive mediators. One potentially important group of such mediators is the kinins, which act through stimulation of G protein-coupled B\textsubscript{1} and B\textsubscript{2} receptors. Interestingly, the nociceptive changes have been shown to be inhibited by pharmacological blockade or gene ablation of B\textsubscript{1} receptors, but refractory to B\textsubscript{2}
receptor. On the other hand, systemic treatment with either B₁ or B₂ receptor antagonists i.e., des-Arg(9)-Leu(8)-BK (HOE 140) have been reported to inhibit tactile allodynia induced by SNL in rats (Werner et al., 2007). Further, intracerebroventricular administration of the B₂ receptor antagonist HOE 140 is documented to inhibit heat hyperalgesia and hyperthermia induced by central injection of lipopolysaccharide (LPS) in rats (Walker et al., 1996). SNL have been shown to increase the expression of B₁ and B₂ receptor proteins in ipsilateral L₄-L₆ spinal nerves and of B₂ (but not B₁) receptor mRNA in L₅ DRG (Lai et al., 2006). Therefore both peripheral and central kinin B₁ and B₂ receptors appear to represent complementary targets through which selective antagonists can attenuate the enhanced responsiveness of the animals to cold, heat and (to a lesser extent) tactile stimuli in neuropathic pain model.

3.II.F.12. Melanocortin Receptor 4 (MC₄) Antagonists

The melanocortins comprise a group of natural peptides derived from the precursor molecule pro-opiomelanocortin (POMC). In the anterior lobe of the pituitary gland, POMC is processed to form the melanocortin and adrenocorticotropic hormone (ACTH), α-MSH and β-MSH. In peripheral tissues, direct effects of melanocortins on the nervous system have been described as early as the late 1950s. Intracerebroventricular (i.c.v) administration of 0.1–10 mg α-MSH in rats has been shown to induce hyperalgesia in the tail-flick test, an effect lasting for 20 (0.1–1 µg) to 80 (10 µg) min (Ulugol et al., 2006). So far, five melanocortin receptor subtypes have been identified that are the members of the G-protein-coupled receptor superfamily. Of these five subtypes, the melanocortin MC₃ and melanocortin MC₄ receptors are expressed in the nervous system. MC₄ receptors are expressed most abundantly in the superficial dorsal horn (lamina I and II) and in the grey matter surrounding the central canal (lamina X), areas that are important in nociceptive transmission (Ulugol et al., 2006). It has been demonstrated that changes in the spinal cord melanocortin system occur after chronic constriction injury of the sciatic nerve in rats. The anti-allodynic effect of the melanocortin receptor antagonist SHU9119 has been documented that is suggested to be caused by a blockade of an endogenous α-MSH-induced tone (Chu et al., 2012).

3.II.F.13. Ephrin-B (Eph-B) Receptor Antagonists
Receptor tyrosine kinases (RTKs) play vital role in transmitting external signals to the inside of many types of cells. Eph-receptors constitute the largest subfamily of RTKs in the human genome, with 13 members divided into an A-subclass (Eph-A1 to Eph-A8) and a B subclass (Eph-B1 to Eph-B6). Their ligands, the ephrins, are also divided into two subclasses: ephrin-A1 to ephrin-A5 and ephrin-B1 to ephrin-B3. Eph-B receptors can also regulate the development of glutamatergic synapses and their plasticity in adult nervous system by interaction with NMDA receptors. Ephrin-B (Eph-B) receptor signaling plays a critical role induction and maintenance of neuropathic pain by regulating neural excitability and synaptic plasticity in the dorsal root ganglion (DRG) and the spinal dorsal horn neurone. Intrathecal application of blocker of Eph-B receptors, Eph-B1-Fc and Eph-B2-Fc chimeras inhibit the induction and maintenance of nerve injury-induced thermal hyperalgesia and mechanical allodynia (Song et al., 2008). Ephrin-B3 is expressed in myelinated oligodendrocytes and inhibits neurite outgrowth in-vitro to an extent similar to myelin-associated glycoprotein (Song et al., 2008). Thus, ephrin-EphB receptor signaling may also be involved in inhibitory effects of myelin during neural regeneration. It has been suggested that Eph-B receptors can modulate acute inflammatory pain processing (Zhao et al., 2010) and nerve crush-induced mechanical allodynia (Kobayashi et al., 2007). This blocking action of ephrin-Eph-B signaling after nerve injury may have dual therapeutic effects, enhancing axonal regeneration and symptomatic relief of neuropathic pain.

3.II.F.14. Protease Activated Receptor (PAR) Antagonists

Protease activated receptors (PARs), a member of guanine nucleotide-binding protein family, have been determined as switch buttons between neuron and glia in many physiologic and pathologic processes, including brain trauma (Jian et al., 2009). PARs participate in the initiation and maintenance of neuropathic pain and play a key role in mediating the interactions of nerve cells. Firstly, following nerve injury, alterations in neuron and neuron function induce an abnormal increase of some neurotransmitters and neuromodulators, such as substance P (SP), calcitonin gene-related peptide (CGRP), prostaglandins, kinins, and so on. Such abnormal factors can act on neuron reversely and then induce pain sensation directly, or activate glial cells (astrocytes and microglia) mediated by PARs, which trigger and accelerate the progression of neuropathic pain. Secondly, when the noxious factors
invade, glial cells are activated as the first barrier of nervous system and secrete many neuroinflammatory factors. Finally, in the progress of neuroinflammatory pain, microglia is activated first and initiates the status of pain, and then inflammatory factors and complements from microglia activate astrocytes and maintain or make the pain worse (Jian et al., 2009; Zhang et al., 2011a). Some studies have identified PAR₂ as an important contributor in inducing astrocytes and microglia abnormal activation, which is one of the main causes of neuropathic pain (Roka et al., 2007). Activation of PAR₂ in peripheral terminals appears to trigger neurogenic inflammation, nociception or hyperalgesia (Lam and Schmidt, 2010; Zhang et al., 2011a). The administration of selective PAR2 antagonist i.e., FSLLRY-amide has been reported to attenuate paclitaxel-induced neuropathic pain in mice thereby indicating potential role of PARs in neuropathic pain (Chen et al., 2011).

3.II.G. Enzyme Inhibitors

3.II.G.1. Cytosolic Kinase Inhibitors

The multiple kinase activation is reported to induce the neuropathic pain via modulation of various cellular process and different cellular signaling pathways. Various kinase inhibitors have been studied in different kinds of neuropathic pain models (Anand et al., 2011; Han et al., 2011). Intrathecal injection of PI₃K inhibitor i.e., wortmannin and LY294002; PKB/Akt inhibitor i.e., Akt inhibitor IV and (-)-Deguelin have been reported to reduce L₅ spinal nerve ligation-induced neuropathic pain in rats (Xu et al., 2007). The intrathecal administration of Cdk5 inhibitors i.e., roscovitine and ERK (MEK) inhibitor i.e., U-0126 have been documented to ameliorate the repetitive nerve stimulation-induced post-inflamatory hyperalgesia and allodynia in rat (Peng et al., 2009). The administration of PDGFR-dependent tyrosine kinase inhibitor i.e., [(3,5-di-tert-butyl-4-hydroxybenzylidene)-malononitrile] (AG17) has been reported to attenuate sciatric nerve ligation-induced neuropathic pain in mice (Narita et al., 2005). The administration of protein kinase A (PKA) inhibitor i.e., Walsh inhibitor peptide (WIPTIDE) has also been documented to ameliorate chronic ethanol ingestion-induced painful peripheral neuropathy in female rats (Dina et al., 2007). Intracerebroventricular (i.c.v.) administration of protein kinase A (PKA) inhibitor i.e., H-89 (N-[2-[[3-(4-Bromophenyl)-2-propenyl]amino]ethyl]-5-isoquinolinesulfonamide) has been reported to show beneficial effects on partial peripheral nerve ligation-induced neuropathic pain in mice (Takasu et al., 2009). The dual inhibitors of protein kinase Cε i.e.,
PKCε-I and ERK1/2 i.e., PD98059 (2′-amino-3′-methoxyflavone) and U0126 (1,4-Diamino-2, 3-dicyano-1, 4-bis (2-aminophenylthio) butadiene) have been documented to attenuate chronic ethanol ingestion-induced painful peripheral neuropathy in rats (Dina et al., 2007). Supraspinal administration of selective PKC inhibitor i.e., calphostin C has been observed to attenuate oxaliplatin-induced painful peripheral neuropathy in rats (Norcini et al., 2009). Intra-thecal administration of PKCγ inhibitor i.e., chelerythrine has been noted to attenuate chronic constriction injury of the infraorbital nerve (ION-CCI)-induced trigeminal neuropathic pain in rat (Nakajima et al., 2011). Administration of Src (sarcoma) activated tyrosine kinase (SFK) inhibitor i.e., 4-amino-5-(4-chlorophenyl)-7-(t-butyl)pyrazolo[3,4-d]pyrimidine (PP2) has been shown to suppress the peripheral nerve injury-induced mechanical hyperalgesia in rat (Katsura et al., 2006). The intrathecal, intraneural and perineural injection of ERK or MEK kinase inhibitor i.e., U0126 has been evidenced to attenuate chronic constriction injury-induced mechanical allodynia and thermal hyperalgesia in rats (Han et al., 2011; Jaggi and Singh, 2011b) as well as in mice (Kiguchi et al., 2009). Administration of calcium/calmodulin-dependent protein kinase-II (CaMK-II) inhibitor has been shown to reduce the partial sciatic nerve ligation-induced neuropathic pain in rat (Wang et al., 2011b). Further, intrathecal administration of Janus activated kinase (JAK)-signal transducers and activators of transcription 3 (STAT-3) signalling inhibitor i.e., flavopiridol (also known as cell cycle inhibitor) has been reported to reduce the spinal nerve injury-induced neuropathic pain in rats (Tsuda et al., 2011). Recently, a clinical trial has reported that the administration of selective p38 mitogen-activated protein kinase (MAPK) inhibitor i.e., dlapmapimod (SB-681323) attenuate nerve trauma, radiculopathy and carpal tunnel syndrome associated neuropathic pain (Anand et al., 2011).

3.II.G.2. Metalloproteinase Inhibitors

Matrix metalloproteinases (MMPs) are a family of zinc and calcium-dependent extracellular proteases that catalyze the degradation of protein components of the extracellular matrix. MMPs contribute to neurodegenerative disorders via degradation of neurovascular barriers, facilitation of immune cell migration and demyelination. MMPs have been implicated in regulating neurovascular permeability and demyelination in patients with symptomatic neuropathy (Teles et al., 2007). MMPs go through a post-transcriptional process
of cleavage and activation, enabling the targeted degradation of their substrate. The regulation of MMP activity is a complex and finely tuned process in which both specific inhibitors (tissue inhibitors of metalloproteinases) and the regulation of afferent pathways at production and activation levels play an important role in neuropathic pain (Kobayashi et al., 2008). Inflammatory cytokines such as IL-1 and TNFα have reported to contribute to regulate the MMPs processes. Fibronectin, collagen type IV and tissue inhibitor of metalloproteinase (TIMP-1) protein are produced mainly by peripheral nerve pericytes, indicating that the basement membrane of the blood–nerve barrier (BNB) is regulated mainly by these cells. Furthermore, in diabetic condition advanced glycation end-products (AGEs) have been shown to increase the amount of fibronectin, collagen type IV and TIMP-1 in pericytes through a similar upregulation of autocrine VEGF and transforming growth factor (TGF)-β released by neuronal pericytes (Shimizu et al., 2011). The intrathecal injections of MMP-9 inhibitor i.e., Inhibitor-I and MMP-2 inhibitor i.e., Inhibitor-III have been reported to attenuate peripheral nerve injury-induced allodynia in rats (Kawasaki et al., 2008). Further, the administration of MMP inhibitor i.e., GM6001 and selective gelatinase inhibitor i.e., SB-3CT have also been shown to ameliorate the spinal cord and peripheral nerve injury-induced neuropathic pain in rat (Kobayashi et al., 2008; Zhang et al., 2011).

3.II.G.3. Protease Inhibitors

The activation of proteolytic enzymes plays a key role in the pathogenesis of toxic neuropathy. The proteolytic enzymes have a role in the degradation of neurofilament (NF) in peripheral nervous system. The degradation of NFs by proteases normally occurs at the levels of nerve terminal, and a degraded cellular material is normally transported back to the cell body for further processing. The processes take place by alterations of calcium-activated neutral protease (calpain) enzyme. Calpains, a family of neutral cytosolic Ca\(^{2+}\)-dependent cysteine proteases, are known to hydrolyse cytoskeletal proteins including NFs. The neuronal proteases especially calpains can induce the neuropathic pain via degradation/degeneration of cytoskeletal proteins (Song et al., 2009). The relationship between the activation of proteolytic enzymes and the specific proteolytic pathways of NF and regulating mechanisms is still unknown. The neutral protease (calpain) inhibitor i.e., MDL-28710 has been demonstrated to block the early expression of local pro-inflammatory cytokine gene in chronic...
constriction nerve injury (CCI) of sciatic nerve-induced neuropathic pain in mice (Uceyler et al., 2010).

3.II.G.4. D-amino Acid Oxidase (DAO) Inhibitors

D-Amino acid oxidase (EC 1.4.3.3, DAO) is a peroxisomal flavin adenine dinucleotide (FAD) containing enzyme that catalyzes with strict stereospecificity the oxidative deamination of neutral and polar D-amino acids yielding hydrogen peroxide and an imino acid. It is widely expressed in the kidneys, liver, and central nervous system (CNS) including the spinal cord (Zhao et al., 2010a). Physiologically D-amino acids play an important role in the regulation of many processes such as aging, neural signaling, and hormone secretion, whereas excess of some D-amino acids in mouse brain tissues provides long-term potentiation of nervous system in the hippocampus and supports spatial learning (Zhao et al., 2010a).

Intravenous administration of the DAO inhibitor i.e., sodium benzoate is reported to ameliorate mechanical hyperalgesia in formalin-induced nociception in rats and in mice (Williams and Lock, 2005). Another non-specific DAO inhibitor i.e., chlorpromazine has been reported to block formalin-induced hyperalgesic response (Hulsebosch et al., 2009). Further, a DAO inhibitor, SEP-227900 has also documented in early stage clinical investigation for the treatment of neuropathic pain (Williams, 2009). In addition, intrathecal administration of potent and selective DAO inhibitor i.e., AS057278 blocked the formalin-induced hyperalgesia in a dose-dependent manner in rats (Ying-Luan et al., 2007; Zhao et al., 2010a). Putative mechanism of DAO in pain involves generation of high amounts of \( \text{H}_2\text{O}_2 \) in the spinal cord, D-alanine, and glycine (Zhao et al., 2010a). Spinal \( \text{H}_2\text{O}_2 \) has been reported to be involved in central sensitization-mediated pain states including neuropathic pain (Lee et al., 2007). Recently, spinal administration of DAO inhibitors has been reported to reduce the tight L5/L6 spinal nerve ligation-induced neuropathic pain in rats (Zhao et al., 2010a).

3.II.G.5. Anandamide Re-uptake and Fatty Acid Amide Hydrolase (FAAH) Inhibitors

Anandamide is also known as an endogenous cannabinoid neurotransmitter and is structurally similar to that of tetrahydrocannabinol (the active constituent of cannabis). Anandamide and other bioactive long-chain N-acylethanolamines (NAE) are formed via
direct release from N-acyl-phosphatidylethanolamine by phospholipase-D (Ueda et al., 2010). In physiological conditions, endogenous anandamide has key role in the short- and long-term control of synaptic transmission. In pathological conditions such as cell damage, shock, neurological disorders, pain and inflammation endocannabinoid levels are noted to be altered. Endocannabinoids have generally been considered to provide neuroprotection, through actions at CB receptors. In contrast, excess production of anandamide has also been reported to induce potential tissue damage. Anandamide-induces calpain activation in the neuronal cells and also causes the cytochrome-C release from mitochondria, subsequently increasing the caspase activity eventually leading to neuronal apoptosis and cell death (Movsesyan et al., 2004). Further the administration of calpain and fatty acid amide hydrolase inhibitor has been shown to ameliorate the anandamide mediated neuronal damage. N-arachidonoylethanolamide (AEA) and 2-arachidonoylglycerol (2-AG) are reported to modulate the neuropathic pain response produced by CCI of the sciatic nerve (Kinsey et al., 2009) and spinal cord contusion models in rats (Baker and Hagg, 2005).

Systemic administration of endocannabinoid uptake inhibitors (VDM-11, OMDM-2, UCM-707 and LY2318912) and FAAH inhibitor (N-arachidonoyl-serotonin, AA-5-HT) have been shown to possess therapeutic potential via increasing endocannabinoid levels (Guindon and Hohmann, 2009). Mixed cannabinoid receptor agonists (levonantradol, WIN55,212-2 and CP,55,940) have also been shown to increase the levels of endocannabinoids and produce CB1-mediated anti-nociceptive effects (Ashton and Glass, 2007). Moreover, intrathecal administration of FAAH inhibitor (URB597/AA5-HT) and MGL-preferring nhibitors (URB602) have also been suggested to provide ameliorative effect on stress-induced algesia (Suplita et al., 2006). Intraplantar (i.pl.) administration of exogenous AEA or the FAAH inhibitor (URB597) is noted to increase the local level of AEA in the model of bone cancer pain (Shingo et al., 2009). FAAH inhibitors (AA-5-HT, PMSF, PTK, URB597, OL-135, octylsulfonyl fluoride) with varying degrees of selectivity also produce antinociceptive effects in the CCI model (Guindon and Hohmann, 2009). Further, AM404 an anandamide re-uptake and transport inhibitor has been reported to enhance the anti-nociceptive effect in chronic constriction injury (CCI) of sciatic nerve induced neuropathic pain in rats (La Rana et al., 2008).
3.II.G.6. Aldose Reductase (AR) Inhibitors

In diabetic condition, long lasting hyperglycemia causes diabetic microvascular complications such as retinopathy, nephropathy as well as neuropathy. One of the key mechanisms is the activation of polyol pathway. In normal physiological conditions glucose is phosphorylated by hexokinase, whereas in hyperglycemic conditions the excess glucose becomes the substrate to initiate the polyol pathway. Polyol pathway comprises two consecutive steps, in the first rate limiting step, reduction of glucose to sorbitol takes place with the help of aldose reductase that requires NADPH as the cofactor. The second step is the reduction of sorbitol to fructose by sorbitol dehydrogenase with NAD+ as the cofactor. Preclinical studies have reported that the administration of aldose reductase inhibitors i.e., ranirestat (AS-3201) and zenarestat suppresses streptozotocin (STZ)-induced diabetic neuropathy in rats (Shimoshige et al., 2009). Some clinical reports have also documented beneficial effect of epalrestat in diabetic neuropathic patients (Kawai et al., 2010).

3.II.G.7. Sorbitol Dehydrogenase (SDH) Inhibitors

In clinical and experimental diabetes, utilization of the sorbitol pathway is substantially increased. In this pathway, glucose is first reduced to sorbitol by aldose reductase and sorbitol then converted to fructose by sorbitol dehydrogenase. Sorbitol pathway plays a key role in the diabetes-induced micro and macro-vascular as well as neuronal complications. Generally sorbitol pathway is altered in the abnormal metabolic conditions like diabetes (Schmidt et al., 2005). Sorbitol dehydrogenase inhibitors have been suggested to be useful in neurovascular complications by number of ways such as: (1) inhibition of sorbitol-exaggerated osmotic stress; (2) alterations in the absolute amounts or ratio of NADPH/NADP⁺ and NADH/NAD⁺, two cofactors that are required for the first (glucose to sorbitol) or second (sorbitol to fructose) steps of the sorbitol pathway and which also contribute to numerous biochemical reactions in the complex diabetic ganglionic milieu; (3) decreased formation of fructose, which could serve as a potential substrate for glycolysis or have osmotic effects; and, (4) modulation of hyperglycemia-induced overproduction of mitochondrial superoxide with resultant decreased glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity (Schmidt et al., 2005). Administration of sorbitol dehydrogenase inhibitors such as SDI-158; SDI-711 has been shown to possess a significant
protective roles in the diabetic autonomic neuropathy (Chu-Moyer et al., 2002; Schmidt et al., 2005). Since only limited studies have done so far, therefore efficacy of sorbitol dehydrogenase inhibitors in neuropathic pain demands further investigations.

3.11.1. Others

3.11.1.1. AGE and RAGEs Modulators

Advanced glycation end products (AGEs) are generated by aging and hyperglycemia and their generation is highly accelerated in the long standing diabetic conditions. The formation and accumulation of AGEs has been implicated in the progression of various disease including neuropathy (Shibasaki et al., 2010). AGEs can induce intracellular damage and apoptosis leading to morphological and functional changes in the nervous system and vital organ. Some studies have reported that AGE breakers i.e., ALT-711, alagebrium and glycation inhibitors i.e., benfotiamine, pyridoxamine, pimagedine, OPB-9195, alpha-lipoic acid, taurine, aminoguanidine, aspirin, carnosine and resveratrol are able to decrease the adverse neuro vascular effects of glycation. The inhibition of pathological responses mediated by AGEs may have therapeutic potential for diabetic neuropathy (Shimizu et al., 2011).

Receptors for AGE (RAGE) have been demonstrated to be located on hematopoietic cells, endothelial cells, as well as spinal motor neurons and cortical neurons. RAGE being one of the major receptors for pro-inflammatory cytokine high mobility group box-1 (HMGB-1) has been shown to be expressed in the primary afferent neurons and SGCs in the DRG, as well as in Schwann cells in the spinal nerve (Shibasaki et al., 2010). HMGB-1 has the pathological role in the development of peripheral nerve injury (spinal nerve ligation) induced pain hypersensitivity. The Immunohistochemistry analysis revealed the induction of HMGB-1 mRNA expression in the primary afferent neurons and satellite glial cells (SGCs) in the DRG, and in Schwann cells in the spinal nerve. Neutralizing antibody against HMGB-1 successfully alleviated the spinal nerve ligation induced mechanical allodynia (Shibasaki et al., 2010). Pharmacological interventions may help counteracting the deleterious effect of RAGE in patients via reduction of AGE formation by AGE breakers and glycation inhibitors and prevention of AGE-RAGE interaction. Heparin binds to RAGE without inducing inflammation, suggesting that it may be applicable as a RAGE blocker (Pestronk et al., 2010). Moreover, another RAGE modulator i.e., methylene bis [4,4-(2 chlorophenylureido...
phenoxyisobutyric acid)] (LR-90) and RAGE antibodies have been shown to ameliorate the neuropathic pain (Figarola et al., 2007).

3.II.H.2. Neuropeptide Modulators

Primary sensory neurons express a number of peptides that act as neurotransmitters and/or neuromodulators. After peripheral axotomy, neuropeptides such as substance P, calcitonin gene-related peptides (CGRP), and somatostatin which are abundantly present in sensory neurons have been shown to be downregulated. On the other hand, neuropeptides such as vasoactive intestinal peptide (VIP), galanin, neuropeptide Y (NPY), cholecystokinin (CCK), and pituitary adenyl cyclase activating polypeptide (PACAP) etc which normally expressed at low levels in sensory neurons, are dramatically increased. Neuropeptides, such as galanin, neurokinin A, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), neurotensin (NT) and cholecystokinin (CCK) are reported to modulate afferent barrage and the functional changes taking place in the spinal cord after a peripheral nerve trauma (Kingery, 2010). Nerve trauma induces synthesis and excessive release of some other peptides, such as neuropeptide Y, from primary afferents which leads to prolonged depolarization of secondary afferents. The peripheral nerve trauma-induced afferent barrage is also likely to be mediated by peptides like substance P, which can induce central sensitization. Intrathecal injection of substance P or somatostatin at the time of nerve transaction enhances the autotomy (Beaudry et al., 2011). Neuropeptides also have supraspinal sites of action. For example, intracerebroventricularly administered neurotensin (NT) increases, whereas CCK decreases autotomy after dorsal rhizotomy (Kumamoto et al., 2011). Another peptide that may decrease neuropathic pain is calcitonin. Continuous intracerebroventricular administration of calcitonin has been shown to decrease autotomy behavior after dorsal rhizotomy. Analogously, systemically administered calcitonin decreases ‘phantom limb pain’ in humans (Eichenberger et al., 2008). The administration of sumatriptan, a calcitonin gene-related peptide (CGRP) release inhibitor, has been reported to possess an ameliorative potential in nociceptive pain sensation in streptozotocin-induced diabetic mice (Khan et al., 2008).

The subcutaneous administration of CI 988 (a selective antagonist of the CCK-2 receptor) has been shown to produce ameliorative effect in unilateral transection of the sciatic
nerve-induced autotomy behavior and on T3 hemisection mediated mechanical allodynia in rats (Gustafsson et al., 1998; Kim et al., 2009a). The administration of CCK receptor antagonists such as lorglumide and PD135,158 has been documented to produce the anti-analgesic action via elimination of dynorphin and activation of ascending pathway in the brain and a descending pathway in the spinal cord (Rady et al., 1999; DeSantana et al., 2010). Clinically the cholecystokinin (CCK) B antagonist L-365,260 has been reported to produce the beneficial effects in intractable non-cancer pain (Ma et al., 2006; McCleane, 2002). Further, administration of peptide ligand i.e., H-Tyr-DPhe-Gly-DTrp-NMeNle-Asp-Phe-NH(2) (RSA 601) for the CCK-2 receptor has been shown to produce anti-nociceptive action (Hanlon et al., 2011).

3.II.H.3. Neurotrophic Factor Modulators

Neurotrophic factors are molecules that promote survival, growth and maintenance of discrete populations of neurones. They have been mostly studied for their developmental effects, and it is now clear that some of these factors are absolutely necessary for normal neuronal development. One important family of neurotrophic factors, the neurotrophins (consisting of nerve growth factor [NGF], brain-derived neurotrophic factor [BDNF], neurotrophin [NT]-3 and NT-4/5) has been shown to support the survival and growth of distinct groups of primary sensory neurons. In addition, the neurotrophins appear to regulate the development of normal functional properties of sensory neurones, such as their ability to respond to peripheral stimuli (Dong et al., 2006). Another family of trophic factors which is also known to have particularly important effects on primary sensory neurons are glial derived neurotrophic factor (GDNF) family. An increase in the levels of BDNF has also been reported to contribute significantly to neuropathic pain as administration of an anti-BDNF antibody substantially reverses the mechanical hypernociceptive state in the brachial plexus avulsion model in mice (Quintao et al., 2008). The nerve damage that precipitates neuropathic pain leads to many changes in sensory neurons, including alterations in putative neurotransmitters/modulators, receptors, ion channels, structural proteins, and anatomic terminations. The relative contribution of each of these to neuropathic pain is currently unknown. Intrathecal infusion of GDNF treatment prevented the emergence of the signs of neuropathic pain in partial ligation of one sciatic nerve. Neurotrophins NGF and NT-3 have
also been noted to ameliorate both mechanical and thermal hyperalgesia, in L5 spinal nerve ligation (Wilson-Gerwing et al., 2005) as well as CCI (Dong et al., 2006). Furthermore, in a double-blind clinical trial, NGF has been found to be beneficial in HIV neuropathy (Pradat, 2003).

3.II.H.4. Complement Cascade Modulators

The components of the complement cascades include proteolytic pro-enzymes, whose sequential activation produces the complement response. Three different cascades can activate complement: the classical pathway, the lectin pathway and the alternative pathway. All three pathways generate C3 convertases that cleave C3 protein into C3a and C3b. C3b participates in a self-amplification loop via the alternative pathway, and it also interacts with C3 convertase to produce C5 convertase, which cleaves C5 into C5a and C5b. C5b then interacts with C6 and C7 to form the C5b-7 complex. C8 and C9 are then recruited to C5b-7 in the membrane to form a membrane attack complex (MAC) so as to damage host cells (Levin et al., 2008).

Three different gene expression assays consistently demonstrate that the levels of multiple complement-cascade related products comprising innate immunity change in the spinal nerve ligation-induced neuropathic pain and the changes have been ameliorated by the administration of non-steroidal anti-inflammatory drugs (Levin et al., 2008). The transcriptional regulation of multiple complement components suggests that the modulators of complement cascades may play an important role in the management of the neuropathic pain. Cobra venom factor (CVF) an inhibitor of complement cascade has been reported to possess the beneficial effect on spinal nerve ligation-induced neuropathic pain in rat (Levin et al., 2008). The numerous drugs have reported the therapeutic action in painful neuropathy by inhibition of the complement pathway. The real-time PCR results have shown the induction of mRNAs for complement components C1q, C3, and C4, in different models of neuropathic pain (Levin et al., 2008). In addition, Twining et al. have demonstrated that chronic bilateral neuropathic pain induced by sciatic inflammatory neuritis, chronic constriction injury and intrathecal activation of glia is alleviated by intrathecal soluble complement receptor-1 (sCR1) injection (Twining et al., 2005). Moreover, the systemic injection of sCR1 has also
been documented to alleviate partial ligation of sciatic nerve induced thermal and mechanical pain (Li et al., 2007).

3.II.H.5. Cytokine Modulators

Spinal nerve transection has been demonstrated to increase NF-κB, TNF-α and IL-1β expression in the brain and the timing of this increase is correlated with the development of neuropathic pain. IL-10 expression is noted to be increased gradually and is associated with the relief of allodynia and hyperalgesia. Further, glucocorticoid betamethasone administration significantly reduced behavioral responses and cerebral levels of NF-κB, TNF-α, IL-1β, and IL-10 and the changes in these specific cytokines appeared to be coincident with pain behavior post-transection. Taken together, the above results suggest that NF-κB and other cytokines may be mediators in the development of neuropathic pain, and that the long-acting analgesic effect of betamethasone treatment is due to its modulation of various cytokines in the CNS (Xie et al., 2006).

Several lines of evidence have demonstrated that Wallerian degeneration following nerve injury contributes to the development of neuropathic pain via production of cytokines and nerve growth factors. Among them, tumor necrosis factor-alpha (TNF-α) appears to play a key role in induction of neuropathic pain following nerve injury. Behavioral studies have demonstrated that intramuscular, subcutaneous, or endoneurial injection of TNF-α produces allodynia and hyperalgesia, while inhibition of TNF-α synthesis or antagonism of TNF-α receptors reduces neuropathic pain behaviors (Leung and Cahill, 2010). Injury of the sciatic nerve leads to upregulation of TNF-α protein and TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2) in DRG and spinal dorsal horn. Tumor necrosis factor-α proteinase inhibitor (TAPI) has been reported to inhibit the activation of TNF-α by chelating TNF-α converting enzyme (TACE) and at higher dose it has also been reported to inhibit the MMP-9 and other MMPs. The inhibition of MMP has been documented to improve the electrophysiologic changes i.e., enhance the nerve conduction velocity and motor performance (Hsu et al., 2006). The administration of TNF-α inhibitor i.e., propentofylline has been reported to ameliorate the spinal nerve transection-induced allodynic pain behavior in rat (Tawfik et al., 2007). The intrathecal administration of fusion protein of TNF-α blocker i.e., etanercept has been documented to attenuate the T13 spinal cord hemisection-induced mechanical allodynia in...
rats (Marchand et al., 2009). In a clinical study, the subcutaneous administration of etanercept has been shown to produce ameliorative effect in severe sciatic related neuropathic pain (Genevay et al., 2004). Similarly, infliximab i.e., an antibody to TNF-α has also been reported to produce beneficial effect in the management of neuropathic pain (Karppinen et al., 2003). The administration of another TNF-α inhibitor i.e., thalidomide and methotrexate has been reported to attenuate chronic constriction injury of sciatic nerve-induced hyperalgesia in rat and neuropathic pain in human (Leung and Cahill, 2010).

3.II.H.6. Glial Cell and Gap Junction Modulators

Gap junctions are specialized intercellular connection channels between the membranes of adjacent cells that allow the ions movements and other small molecules (i.e., cAMP, inositol-1,4,5-triphosphate (IP3), ATP and small peptides) between the cells in the nervous system. Gap junction connectivity is one of the major mechanisms for the development of neuropathic pain via activation of remote glial cell (i.e., astrocytes) gap junction at the site of injury (Roh et al., 2010). In addition, activated astrocytes due to rapid electrical responses to neuronal activity trigger the intercellular propagation of Ca\(^{2+}\) waves via gap junction channels. Further, it has also been proposed that activated astrocytes and gap junction channels can induce the release of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6 that contribute to the excitation of nervous system and development of chronic maladaptive neuropathic pain (Yao et al., 2011).

Carbenoxolone (CARB) has gap junction blocking property and it has been reported to reduce the spinal cord injury-induced development of bilateral thermal hyperalgesia and mechanical allodynia, along with reduced expression of glial fibrillary acid protein (GFAP) and NR1 subunit phosphorylation in rats (Roh et al., 2010). CARB is reported to possess ameliorative role in formalin-induced neuronal hyperactivity, thermal pain sensation, zymosan-induced neuritis, chronic constriction injury of sciatic nerve induced neuropathic pain, thrombus-induced ischemic pain, and spinal cord injury induced neuropathic pain (Seo et al., 2008; Roh et al., 2010). Several studies have demonstrated the involvement of gap junctions along with glial cell activation in the development of chronic pain such as inflammatory, peripheral and central neuropathic pain (Zhang et al., 2009). Glial cells contribute to the induction of chronic neuropathic pain sensation in brain via gap junction
modulation. Direct metabolic inhibitors of glia, such as minocycline and propentofylline, have been shown to be anti-nociceptive in rats (Tan et al., 2009).

3.II.H.7. Nitrous Oxide (N₂O) Modulators

Nitrous oxide (N₂O) is a common analgesic and anesthetic gas with multiple potential targets. *In vitro* and *in vivo* studies have reported that N₂O probably has NMDA receptor blocking actions. Animal studies have shown beneficial effect of N₂O in pain quiet similar to that of NMDA antagonists (Rivat et al., 2007). N₂O could be an efficient strategy for alleviating neuropathic pain in humans particularly for patients whose central sensitization mechanisms are highly developed (Bessiere et al., 2010). It would be of clinical interest to know whether N₂O exposure may potentiate the analgesic effects of drugs that are generally used for alleviating neuropathic pain. Various drug classes possess the anti-nociceptive action via modulating nitrous oxide pathway such as acetyl choline, morphine, opioids, Loperamide, NSAIDs, statins, gapapentin, PPAR-γ agonists, α₂-adrenoceptor agonist xylazine, phosphodiesterase inhibitors, melatonin, anesthetic gas nitrous oxide (Hervey et al., 2009; Cope et al., 2010). The nitrous oxide modulators have been shown to possess diverse role in the management of neuropathic pain based on the concentration, time of treatment and route of administration (Cury et al., 2011).

3.II.H.8. Antibiotics

Several antibiotics have been shown to possess good immunomodulatory action. The possibility that antibiotics may be useful for treating neuropathic pain appears to be wayward but there are at least two possible mechanisms where this class of medications may work. After nerve damage, activated microglia cells release pro-inflammatory cytokines that sensitize surrounding neurons and cause chronic pain persistence (Chong and Brandner, 2006) and certain drugs including the antibiotic have been shown to antagonise this action. The second interesting observation is that many β-lactam antibiotics like ceftriaxone stimulate the expression of glutamate transporter protein (GLT1) (Lee et al., 2008). The transport of glutamate out of synaptic clefts into astroglia cells may be important for modulating
nociceptive neurotransmission. Hence the antibiotics may be useful in management of neuropathic pain.

Tacrolimus (FK506) and sirolimus (rapamycin) are macrocyclic triene antibiotic products of *Streptomyces hygroscopicus*, and are potent immunosuppressive drugs. Both sirolimus and Tacrolimus have been shown to be effective in inflammatory adjuvant arthritis pain model and ischemia reperfusion-induced vasculatic neuropathic pain in rats respectively (Muthuraman and Sood, 2010; Orhan *et al.*, 2010).

Ceftriaxone is a β-lactam antibiotics, commonly used to treat many kinds of bacterial infections, including severe or life-threatening forms of meningitis. It can enter the central nervous system, including the brain and spinal cord, via the blood–brain barrier and modulate the glial glutamate transporter-1 (Lee *et al.*, 2008). This property of β-lactam antibiotics has been shown to provide beneficial effect in amyotrophic lateral sclerosis, stroke, and chronic constrictive nerve injury (CCI) of the sciatic nerve-induced neuropathic pain (Hu *et al.*, 2010).

Spicamycin originally formulated as an anti-tumor antibiotic is produced by the bacterium *Streptomyces alanosinicus* (Weinstein *et al.*, 2011). The non-water-soluble spicamycin derivative KRN5500, produces significant and prolonged decrease in neuropathic pain-related behavior in a number of rat models (Kobierski *et al.*, 2003). It is approved for phase II studies for cancer and produced prolonged and almost complete relief of the neuropathic pain, but not acute nociceptive pain (Weinstein *et al.*, 2011). The removal of the fatty acid moiety in a subclass of spicamycin derivatives results in a water-soluble synthetic spicamycin derivative i.e., SAN-Gly, which can also decrease the spared nerve injury-induced neuropathic pain in rats (Weinstein *et al.*, 2011). The water-soluble formulation of the drug is obviously more amenable for human administration.

Methotrexate is an anti-cancer ("antineoplastic" or "cytotoxic") chemotherapeutic agent; it is used to treat certain types of cancer of the breast, skin, head and neck, or lung. It is also reported to inhibit the glial activation and cause pharmacologically suppression of the spinal microglial cell to produced therapeutic effect in the chronic constriction injury, spinal nerve ligation, and dorsal roots rhizotomy induced neuropathic pain models in rat (Scholz *et al.*, 2008). Moreover, reduction of microglial activation by another antibiotic minocycline has also been reported in the management of neuropathic pain (Ledeboer *et al.*, 2005).
3.III. Recent Therapeutic Approaches

3.III.A. Transplant Therapy

Transplanting cells that secrete neuroactive substances with analgesic properties into the central as well as peripheral nervous system may have therapeutic potential for the long-term treatment of chronic pain. The transplantation of biologic "minipumps" containing GAD67 cDNA (glutamate decarboxylase, the synthetic enzyme for GABA), and the GABAergic cell line, 33G10.17 has been reported to alleviate chronic neuropathic pain via delivering the antinociceptive molecules, such as GABA in chronic constriction injury of the sciatic nerve-induced neuropathic pain model in rat (Lee et al., 2010). The lumbar transplantation of neuronal cell line (RN33B), transfected with genetically modified brain-derived neurotrophic factor cDNA and the BDNF-synthesizing cell line (33BDNF.4) has been shown to reverse the development of chronic neuropathic pain in sciatic nerve constriction-induced pain sensation in rats (Cejas et al., 2000). The intrathecal transplantation of spinal progenitor cell has been demonstrated to alleviate chronic constriction injury (CCI) of the sciatic nerve-induced chronic neuropathic pain via modifying the glutamic acid decarboxylase (GAD) immunoreactivity in rats (Klass et al., 2007). The intrathecal implantation of neuroblastoma cells (NB69) reduces thermal and cold nociceptive sensation in chronic constriction injury of the sciatic nerve-induced neuropathic pain model in rats via increase in the concentrations of dopamine and serotonin metabolites level in the cerebro spinal fluid (de la Calle et al., 2002). The intrathecal transplantation of human proenkephalin gene transfected autologous macrophage has reported that the secretion of proenkephalin in the spinal cord produce ameliorative effect in sciatic nerve constriction-induced hyperalgesia and allodynia in rats (Hino et al., 2009).

3.III.B. Stem Cell Therapy

Stem cell therapy has been considered as one of the novel therapeutic approaches some recent studies have implicated potential of stem cell in neuropathic pain. The transplantation of bone marrow-derived mononuclear stem cells (BM-MNC) has been reported to produce therapeutic effect in sciatic nerve transaction (axotomy)-induced neuropathic pain model via rising the rate and degree of nerve regeneration and remyelination in rats (Goel et al., 2009). The intravenous administration of bone marrow-derived
mononuclear cell (BM-MNC) has also been shown to possess the beneficial effect in chronic constriction injury (CCI) of sciatic nerve-induced neuropathic pain in male Sprague Dawley rats (Klass et al., 2007). The lateral cerebral ventricle transplantation of human mesenchymal stem cells (hMSCs) has been shown to ameliorate spared nerve injury (SNI) induced peripheral neuropathic pain in rats (Siniscalco et al., 2010). Another study showed that the transplantation of embryonic neural stem cell transfected with Fos (+) and NADPH-d (+) neurons ameliorated spinal cord injury hemisection of T12-T13 segments i.e., laminectomy induced neuropathic pain via decrease in NADPH-d and Fos reactivity in rostral and caudal segments of the spinal cord in rat (Dagci et al., 2011). Results of the preliminary studies indicate that stem cell therapy could be a valuable future therapeutic regenerative medicine for neuropathic pain.

3.III.C. Antisense Oligonucleotide Therapy

Antisense oligonucleotides (ASO) are short, single-stranded RNA or DNA sequences that bind to mRNA via hydrogen bonds and inhibit translation or cause degradation of target mRNA. It has been reported that, an increase in phosphorated cyclic AMP response element-binding protein (CREB) in the spinal dorsal horn occur in inflammation pain, neuropathic pain as well as chronic muscle pain (Liou et al., 2009). Studies have documented the role of CREB and pCREB in the maintenance of mechanical and cold allodynia induced by a neuropathic SNI model (Wang et al., 2006). Many pain-related genes which may contribute to central sensitization are activated by CREB, including the immediate early gene c-fos, brain-derived neurotrophic factor (BDNF), calcitonin gene-related peptide (CGRP), the alpha subunit of calmodulin-dependent protein kinase II (CaMKII), and the neurokinin 1 receptor (NK1R). A considerable amount of evidence has indicated that CREB-dependent gene expression is required for long-term changes in the synaptic plasticity induced by various nociceptive stimuli (Alberini, 2009). The expression of GDNF and GFRα-1 (the high-affinity receptor of GDNF) is well documented in dorsal root ganglions (DRG) in a rat model of neuropathic pain induced by chronic constriction injury (CCI) (Dong et al., 2006). Intrathecal administration of antisense oligodeoxynucleotide against GFRα-1 has been shown to cause down-regulation of GFRα-1 expression (Herrmann, 2008). c-Fos expression has been documented in the nerve injury, diabetic and vincristine-induced neuropathic pain models
In the pathogenesis of pain progress C-fos gene play a major role activation of jun-mediated action, modulation of neuropeptide Y (Tsai et al., 2009). The systemic administration of IMT504, the prototype of the PyNNTTTTGT class of immunostimulatory oligonucleotides has been reported to produce sciatic nerve injury-induced nociceptive pain sensation via stimulation of bone marrow stromal cells (MSCs) and reduction of c-Fos expression in rats (Coronel et al., 2008).

3.III.D. Recombinant Therapy (Herpes Vector-Mediated Gene Transfer)

Intrathecal injection of plasmid, adenovirus, and adeno-associated virus–based vectors has been tested in animal models of pain, but the herpes simplex virus (HSV) vectors has been predominatly used for the treatment of chronic pain without the production of any adverse effect. HSV is a human pathogen that naturally establishes a life-long latent infection of human peripheral sensory neurons. Genetically modified recombinant HSV vectors have been constructed that are incapable of replication, but nonetheless efficiently infect and establish a latent-like state in neurons in vitro and in vivo without the ability to reactivate (Manservigi et al., 2010). HSV vectors can be used to transfer and express genes in the nervous system using natural expression mechanisms already present in the virus genome. These products have been designed to modify the structure and/or function of neuronal elements, and represent a novel therapeutic strategy for diseases of the neuropathic pain and neuronal related disorders.

The herpes virus has a natural ability to travel from the peripheral nervous system to the sensory nerve centers (called the dorsal root ganglion) in the spinal cord, so vectors created from the herpes virus are particularly well-suited for treatment of neurological disorders such as peripheral neuropathy (Liu et al., 2009). Genetically modified recombinant herpes viruses able to carry the selected gene sequence and they stay in the sensory nerve centre (Liu et al., 2009).

Opioid receptors are found presynaptically on the terminals of primary nociceptive afferents in the spinal cord, and postsynaptically on second-order neurons in the dorsal horn. Activation of receptors naturally by endogenous ligands enkephalin or endomorphin (EM), or therapeutically by opiate drugs such as morphine inhibits pain-related neurotransmission at the spinal level. The efficacy of HSV-mediated gene transfer of enkephalin has been observed to ameliorate nociceptive pain sensation in rodent model (Glorioso and Fink, 2008).
Subsequently it has been demonstrated that a similar tk-HSV-based vector containing the human proenkephalin gene when injected subcutaneously into the paw reduces hyperalgesic C-fiber responses ipsilateral to the injection (Yeomans and Wilson, 2009). The gene transfer with genomic HSV vectors modified to express nerve growth factor (NGF) can be used to prevent the streptozotocin-induced progression of sensory neuropathy in mice (Wu et al., 2011). Subcutaneous inoculation of the endomorphin (EM) expressing HSV vector into the footpad of rats with neuropathic pain resulted in a significant reduction in mechanical and thermal pain sensation via blockade of the highly selective \( \mu \)-opioid receptor action as confirmed by the highly selective \( \mu \)-opioid receptor antagonist D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-amide (Hao et al., 2005; Glorioso and Fink, 2008). Moreover, [d-Ala2, N-MePhe4, Gly-ol5] enkephalin has been noted to reduce C-fiber nociceptive responses via internalization of the micro opioid receptor in the spinal cord of morphine tolerant rats (Chen et al., 2008). Glutamic acid decarboxylase (GAD) decarboxylates the glutamic acid to produce GABA, subcutaneous inoculation of the GAD-expressing HSV vector transduces DRG neurons to produce GAD and release GABA in the selective spinal nerve ligation and T13 spinal cord hemisection-induced neuropathic pain models (Glorioso and Fink, 2008; Huang et al., 2011a).

Among the proinflammatory substances released by activated microglia and astrocytes in the spinal cord, tumor necrosis factor \( \alpha \) (TNF\( \alpha \)) appears to play a central role. Intraperitoneal inoculation of neutralizing antibodies directed against the p55 TNF receptor (TNFR) reduce thermal hyperalgesia and mechanical allodynia, whereas the intrathecal administration of the recombinant p75 soluble TNFR (sTNFR) peptide (etanercept) reduces mechanical allodynia in a rat model of neuropathic pain (Svensson et al., 2005). IL-4 is a prototypical anti-inflammatory cytokine and HSVexpressing IL-4 is noted to prevent the development of autoimmune encephalitis in Biozzi AB/H mice and in rhesus monkeys (Glorioso and Fink, 2008; Zandian et al., 2011). The analgesic effects of locally HSV vector coded IL-4 and IL-10 have been reported to reduce the neuropathic pain (Zou et al., 2008).

There is substantial evidence from animal studies and human genetics that the voltage-gated sodium channel isoform Nav1.7 and the peptide neurotransmitter calcitonin gene-related peptide play important roles in pain perception in the chronic pain states (Yeomans and Wilson, 2009). Calcitonin gene-related peptide (CGRP) has been shown to be released in
small-diameter nociceptive primary afferent sensory neuron and consequently, induces a nociceptive hyperalgesia. Herpes virus-based vector encoding an antisense sequence of the CGRP clearly reduced CGRP immunoreactivity in the infected spinal dorsal horn neurons. HSV vector coding a sequence antisense to Nav1.7 applied to the skin has been reported to prevent complete Freund’s adjuvant-induced C and A-delta fiber pain sensation via reduction of Nav1.7 expression (Yeomans and Wilson, 2009). Moreover, the HSV vector coding a sequence antisense to CGRP reduces the expression of CGRP in transduced DRG neurons with concomitant reduction in nociceptive neurotransmission in rats (Sarajari and Oblinger, 2010).

Despite of the fact that number of targets are currently being explored, no sure shot remedy exists for neuropathic pain. The major limitation of the existing drug therapy is marginal efficacy and high incidence of side effects. Recently focus has been directed towards drugs from plant origin with the belief that ample scope lie in herbal drugs for the effective management of painful conditions of neuropathy.

3.IV. Pharmacological Interventions Employed in Present Investigations

3.IV.A. Acorus calamus

*Acorus calamus* (Family: *Araceae*) is an indigenous plant commonly known as sweet flag or buch plant. It is grass like, rhizome forming plant can grow 2 meters high, resembling an iris. The plant is a perennial herb growing throughout India, China, Europe, and America. In India it grows in marshy places upto 1800 meters height (Singh *et al.*, 2011).
Fig. 3. Illustration of *Acorus calamus* whole plant and structure of rhizome part.

3.IV.A.1. Traditional Aspects

*Acorus calamus* belongs to the family of Araceae, commonly known as Vacha, has been indicated in the Indian system of medicine. Four types of *Acorus calamus* have been characterized: diploid (North America), triploid (Europe), tetraploid (East Asia, India and Japan) and hexaploid (Kashmir) (Duke, 1985; Muthuraman *et al.*, 2011). The plant is a perennial herb growing throughout India, Europe, Asia and America. *Acorus calamus* has a very long history of medicinal use in many herbal traditions. This plant is mentioned by many
of the great classical writers on medicine, like Hippocrates (460-377 BC) and Theophrastus (371-287 BC). According to Dioscorides, the smoke of *Acorus calamus* (if taken orally through a funnel) relieves cough. For centuries, many native American tribes were familiar with calamus and it had been used as folk medicine. The unpeeled, dried rhizome was listed in the U.S. Pharmacopoeia until 1916 and in the National Formulary until 1950, for medicinal use on humans. As per Indian Ayurveda it has high value as a rejuvenator for the brain & nervous system and also used for digestive disorders, toothache and headaches (Chevallier, 1996). In Indian and Chinese traditional medicines, roots and rhizomes of *Acorus calamus* have been used for the improvement of age-dependent learning performances, and as carminative, expectorant, antifungal, hallucinogenic, hypotensive and sedative (Hazra *et al.*, 2007; Ghosh, 2006).

3.IV.A.2. Phytochemical Reports

*Acorus calamus* contains glycosides, saponins, tannins, mucilage, volatile oil and bitter principles. The main chemical components of *Acorus calamus* are hydrocarbon, asarone, acorenone, calamendiol, α-selinene, α-calacorene, calamusenone, camphone and shyobunone. The essential oil has been shown to contain monoterpene, sequestrine calamenol, calamene, calamenone, methyleugenol and very small quantities of palmitic, heptylic and butylic acids. Moreover, sesquiterpenic ketones and alcohols are also present. Further, two bitter principles i.e., acorin and acoretin, have also been identified in this plant (Duke, 1985).

3.IV.A.3. Pharmacological Reports

The ethanolic extract of *Acorus calamus* has been shown to prevent gastro-duodenal ulcers, whereas aqueous & hydroalcoholic extract express the hypolipidemic and neuropharmacological activities (Rafatullah *et al.*, 1994; Parap and Mengi, 2003). *Acorus calamus* also used in the treatment of digestive complaints, bronchitis, sinusitis etc. Several recent studies have also explored it’s potential usefulness in anorexia nervosa (Phillips and Foy, 1990), skin eruption, rheumatic pain, neuralgia (Tippani *et al.*, 2008), epilepsy (Hazra *et al.*, 2007; Yang *et al.*, 2008) as well as neuroprotective against ischemic and acrylamide induced neuronal insult (Shukla *et al.*, 2002; 2006). Pharmacologically, it has been reported to possess peroxisome proliferator activated receptor (PPAR) agonistic action (Rau *et al.*, 2006),
acetylcholinesterase inhibition (Mukherjee et al., 2007) and free radical scavenging activity (Manikandan et al., 2005). However, its potential in peripheral neuropathy is yet to be explored.

3.IV.B. Pregabalin

Pregabalin [Lyrica\textsuperscript{TM}, (S)-3-(aminomethyl)-5-methylhexanoic acid or S- (+) – isomer of 3 – isobutyl \( \gamma \)-aminobutyric acid] a structural analogue of gamma aminobutyric acid (GABA) (Kumar et al., 2010) and is a selective \( \text{Ca}_v \ 2.2 \) (\( \alpha_2-\delta \) subunit) channel antagonist. It is a well known anti-convulsant agent. In addition to its anti-convulsant property, pregabalin is also known to possess analgesic and anxiolytic actions (Stump, 2009). Studies have demonstrated anti-hyperalgesic and anti-allodynic effect of pregabalin in various animal models of neuropathic pain (Kumar et al., 2010; Bender et al., 2010; Park et al., 2010a). Moreover, pregabalin has also shown good clinical efficacy in painful neuropathic conditions in humans (Martinez et al., 2012; Jensen et al., 2011) and is indeed one of the commonly used clinical agent for neuropathic pain. Pregabalin served as positive standard in the present investigations.