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Review Article

Exploring the Pain Attenuating Potential of Imatinib in Chronic Constriction Injury Model of Neuropathic Pain

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Abstract

Background: Preclinical studies have identified three members of tyrosine kinase receptor family (Trk), TrkA, TrkB, and TrkC in dorsal root of ganglia (DRG), which carry sensory neural signals to the central nervous system from the peripheral nervous system in neuropathic pain. Imatinib is a selective tyrosine kinase inhibitor and widely employed as anti-cancer drug in myeloid leukemia and gastrointestinal stromal tumor. The present study was designed to investigate the potential of imatinib in neuropathic pain.
Method: Neuropathic pain was induced by chronic constriction injury in rats by putting four loose ligatures around sciatic nerve. The extent of neuropathic pain was assessed by noting paw withdrawal threshold (mechanical hyperalgesia) in pin prick test, paw withdrawal latency in hot plate test (heat hyperalgesia) and paw withdrawal duration in acetone drop test (cold allodynia) before surgery and on 14th day post surgery.
Result: There was a significant development of cold allodynia, mechanical and heat hyperalgesia on 14th day in CCI-subjected rats. Administration of imatinib (25 mg/kg and 50 mg/kg) significantly abolished the behavioural deficits (hyperalgesia and allodynia) induced by CCI in a dose-dependent manner.
Conclusion: The observed beneficial effects of imatinib in reduction of behavioral deficits in CCI-subjected rats may be possibly attributed to tyrosine kinase inhibition in dorsal root ganglia neurons associated with the neuropathic pain.

Key words: neuropathic pain; tyrosine kinase; chronic constriction injury; imatinib

Introduction

Neuropathic pain is a chronic pain that arise due to injury or a disease involving somatosensory systems such as traumatic injuries, inflammation, vascular disorders and autoimmune disease [1]. It has been observed that there are more than 30% people of general population affected by persisting pain, which often becomes pathological and debilitating [2] and around 7 in every 100 people over the world have chronic neuropathic pain [3]. The symptoms of neuropathic pain include numbness, tingling, spontaneous pain, hyperalgesia, allodynia, dysthesia and other sensory abnormalities [4-6]. Depending on the location of nerve damage, there are different types of neuropathies including peripheral neuropathy, cranial neuropathy, autonomic neuropathy, diabetic neuropathy, drug induced neuropathy and alcoholic neuropathy [7,8].

The therapeutic approaches for neuropathic pain management consist of calcium channel modulating drugs (gabapentin, pregabalin), tricyclic antidepressants (amitriptyline, nortriptyline, lofepramine, duloxetine), opioids (morphine, oxycodone, propoxyphene) and serotonin-noradrenalin reuptake inhibitors (venlafaxine, duloxetine) as the first-line treatment options for neuropathic pain [9-11]. Recently neurostimulation techniques have also become apparent for the treatment of chronic pain, however effectiveness and safety is still limited, which strengthens the need for new targets to reduce the neuropathic pain.

Imatinib mesylate is a selective protein tyrosine kinase inhibitor, which can inhibit PDGF-R, BCR/Abl, c-KIT, c-fms, TCR/Abl, Lck, FLT-3 and MAPKs activities on various cell types [12]. Imatinib is one of the primary anti-cancer drugs for the traetment of chronic myeloid leukemia and gastrointestinal stromal tumor [13, 14]. However, apart from anticancer activity, studies have shown its broad therapeutic potential in a number of CNS diseases including stroke, Alzheimer disease, spinal cord injury etc [15, 16]. Tyrosine kinases are the family of enzymes, which catalyze phosphorlyation of selected tyrosine residue of the target proteins using ATP. The proteins phosphorylation at tyrosine residues is critical in cellular signal transduction, neoplastic transformation and

control of the mitotic cycle [17, 18]. It has been revealed that there are about 58 receptor tyrosine

kinases (RTKs) and 32 non-receptor types (nRTKs) in the human genome [19]. RTK family includes epidermal growth factor receptors (EGFRs), platelet-derived growth factor receptors (PDGFRs), fibroblast growth factor receptors (FGFRs), vascular endothelial growth factor receptors (VEGFRs), hepatocyte growth factor/scatter factor receptors (HGF/SF), ephrin receptors (Ephs), and the insulin receptors (IRs). Besides their roles as growth factor receptors and in progression of various cancers, these RTKs have been identified in onset and progression of neuropathic pain. In dorsal root of ganglia (DRG), which carry sensory neural signals from the peripheral nervous system to the central nervous system in neuropathic pain, three members of tyrosine kinase receptor (Trk) family, TrkA, TrkB, and TrkC have been identified [20, 21]. Furthermore, anti-inflammatory potential of imatinib in terms of reduction in the levels of cytokines and chemokines including IL-1β, IFN-γ, TNF-α and IL-17 has also been reported [22]. These cytokines and chemokines play key role in inflammation and neuropathic pain by inducing changes in the sensory neurons in DRG and astrocytes. Recently, it has been shown that inhibition of FLT3 tyrosine kinase significantly alleviates neuropathic pain [23]. Katsursa et al (2006) demonstrate that activation of Src kinases in spinal microglia contribute to mechanical hypersenstivity following peripheral after nerve injury [24]. Chen found that Casein kinase 2 regulate N-methyl –D-asparate receptor activity in spinal cord and pain hypersensitivity induced by nerve injury [25]. The specific inhibition of IKB kinase has also been shown to reduce hyperalgesia in inflammation and neuropathic pain model in rats [26]. Considering the distribution of tyrosine kinase receptors in DRG, its possible association with neuropathic pain along with the broad therapeutic potential of imatinib, the present study was designed to investigate the potential of imatinib in neuropathic pain induced by chronic constriction injury in rats.

Material and Method

Experimental animals and Drugs

All experiments were performed in accordance with guidelines approved by the Institutional Animal Ethics Committee (IAEC) (Reg. No. 1407/PO/Re/S/11CPCSEA). Sprague Dawley rats of either sex, weighing 200-250g were purchased from Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar. The animals were housed in the departmental animal house with standard laboratory conditions i.e. temperature, chow diet and normal cycle of 12 hours light and 12 hours dark. The care of the animals was carried out as per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on animals (CPCSEA) Ministry of Environment and Forest, Government of India. Imatinib was procured from Laurus Labs Ltd., Vishakhapatnam, Andhra Pradesh, India and was dissolved in normal saline. It was freshly prepared before use. The doses of imatinib were selected on the basis of previously published studies [27-29].

Induction of Neuropathy pain by Chronic Constriction Injury (CCI)

CCI was performed under anesthesia to induce neuropathic pain [30]. Intraperitoneal injection of ketamine (80 mg/kg) and xylazine (10 mg/kg) was used to anesthetize rats [31]. Following anesthesia, the hair of the rat's lower back and thigh region were shaved carefully and the shaved area was sterilized with three alternate applications of 70% isopropyl alcohol and iodine solution. The cut was made in the left thigh to expose the sciatic nerve. Following exposure, the sciatic nerve was ligated with silk 4-0 thread at four sites with 1 mm gap with appropriate care. The ligation affected approximately 6 mm of nerve length [32]. The wound was closed with sutures in the muscle and the skin. The animal was then allowed to recover from surgery. All surgical procedures were carried out under normal sterile conditions.

Behavioral Examinations

Cold allodynia (Acetone test)

Cold allodynia is an increased sensitivity to normal non-painful cold temperature and it is considered as a characteristic feature of neuropathic pain states. For the assessment of development of cold allodynia, 100µL of acetone was applied on the plantar surface of the paw with the help of appendroff pipette without touching the skin of animal. The response of rat to acetone was noted for 20s and was graded to a 4-point scale as defined by [33], i.e. 0: no reflex; 1: quick stamp, flick or withdrawal of paw; 2: repeated flicking or prolonged withdrawal; 3: repeated flicking with licking of the paw. This same procedure was repeated 3-4 times at 5 min gaps between the acetone applications and the individual scores noted in 20s interval were added to obtain a single score over a cumulative period of 60s. The minimum score was 0, while the maximum possible score was 9 [34].

Heat hyperalgesia (hot-plate test)

The heat hyperalgesia is a useful pain index assessed by measuring the thermal nociceptive threshold on Eddy's hot plate. The animals were placed on hot plate at temperature of 52.5±1.0°C and the withdrawal latency, in terms of jumping or licking of the hind paw was recorded in seconds. The cut-off time was maintained at 15 sec to avoid the injury to paw [35].

Mechanical hyperalgesia (Pin prick test)

The assessment of mechanical hyperalgesia was done by pin prick test to detect a cutaneous pain sensation and to differentiate such sensations from pressure stimuli [36]. The rats were placed into the elevated mesh floored testing cage 15-30 minutes before measuring withdrawal thresholds. The injured surface of the hind paw was touched with the point of a bent gauge needle (at 90º to the syringe) at strength necessary to produce a reflex withdrawal response. The paw withdrawal duration (PWD) was recorded in seconds and the normal quick reflex withdrawal response was given the value of 0.6s.

Experimental Protocol

Total six groups were employed in the present study with five animals in each group.

Group I: Normal group

In normal control group, rats were not subjected to any treatment. The different behavioral tests, including the heat hyperalgesia, cold hyperalgesia and mechanical hyperalgesia were conducted on day 0 (a day before surgery) and 14th day (post- surgery).

Group II: Sham group

In this group, rats were subjected to surgical procedure to expose the left sciatic nerve without any nerve ligation on day 1. The behavioral tests including the heat hyperalgesia, cold hyperalgesia and mechanical hyperalgesia were conducted before doing surgery on day 0 and conducted after surgery on day 14.

Group III: CCI Control

In this group, rats were subjected to the surgical procedures to expose and ligate the left sciatic nerve on day 1 (day of surgery). The pain related all behavioral tests were performed at different time intervals as described in group II.

Group IV and V: Imatinib (25 mg/kg and 50 mg/kg)

In this group, imatinib (25 and 50 mg/kg) was administered in CCI subjected rats for 14 days starting from day 1 (day of surgery). The pain

related behavioral tests were performed at different time intervals as described in group II.

Group VI: Imatinib *per se*

Imatinib (50 mg/kg) was administered in normal rats for 14 days. Further, the pain-related behavioral tests were performed at different time intervals as described in group II.

Statistical Analysis

The results were expressed in mean ± S.D. The data of behavioral tests were analyzed using two-away ANOVA followed by Bonferonni's post hoc test, using Graph pad prism version- 5.0 software. The *P* value < 0.05 was considered to be statistically significant.

Results

Effects of imatinib on cold–allodynia (acetone drop test) in chronic constriction injury-induced neuropathic pain

Chronic constriction injury resulted in significant development of cold allodynia on 14th day after surgery as compared to sham group (**Figure 1)** as measured by acetone drop test. Administration of imatinib (25 and 50 mg/kg, *i.p*) for 14 days significantly attenuated CCI-induced cold allodynia as compared to sham group. The drug was shown produce its actions in a dose-dependent manner in CCI-subjected rats and the effect of imatinib at the dose 50 mg/kg was more significant than the corresponding dose 25 mg/kg. *Per se* administration of imatinib (50 mg/kg) did not modulate cold allodynia in normal rats.

Effects of pharmacological interventions on heat-hyperalgesia (hot plate test) in chronic constriction injury–induced neuropathic pain

Chronic constriction injury significantly decreased the paw withdrawal latency in the hot plate test as compared to sham group **(Figure 2),** signifying the development heat hyperalgesia. Administration of imatinib (25 and 50 mg/kg *i.p*) for 14 days increased the latency of paw withdrawal in CCI-subjected rats in dose-dependent manner. *Per se* administration of imatinib did not modulate heat-related behavioral functions in normal rats.

Effects of pharmacological interventions on mechanical hyperalgesia (pin prick test) in chronic constriction injury-induced neuropathic pain

Chronic constriction injury led to significant increase in paw withdrawal duration in response to pin prick test as compared to sham group **(Figure 3)**, suggesting the development of mechanical hyperalgesia. Administration of imatinib (25 and 50 mg/kg, *i.p*) for 14 days significantly attenuated the CCI–induced increase in withdrawal duration in a dose-dependent manner. *Per se* administration of imatinib did not modulate mechanical pain-related behavioral functions in normal rats.

Discussion

The present study investigated the therapeutic potential of imatinib in an experimental model of neuropathic pain. The study employed chronic constriction injury (CCI) model to induce neuropathic pain [30,37]. CCI is a widely employed model of peripheral sciatic nerve to delineate the mechanisms involved in the development of pain and to explore new drugs for the amelioration of neuropathic pain [38]. In the present study, a significant increase in paw withdrawal response in cold allodynia test was observed in CCI-subjected rats on 14th day after surgery. Further, an increase in the paw withdrawal time during the pin prick test was also observed on the 14th day signifying the development of mechanical allodynia in CCI-subjected rats. Moreover, a decrease in the paw withdrawal time in the hot plate test suggested the development of heat allodynia on 14th day after surgery in CCI-subjected rats. The observed results are in consistent with the previous finding showing the development of neuropathic pain in CCI model [39-42].

In the present study, administration of imatinib (25 and 50 mg/kg) for 14th days produced significant relief from CCI-induced pain in terms of decrease in heat allodynia, cold allodynia and mechanical allodynia in a dose-dependent manner. Imatinib significantly decreased the paw withdrawal response in the cold allodynia test in CCI-subjected rats on 14th day after surgery **(Figure 1).** Further, imatinib treatment significantly attenuated pin-prick evoked exaggerated pain response in terms of decrease in paw withdrawal time during pin prick test in CCI-subjected rats **(Figure 2)**. In addition, imatinib treatment significantly increased the paw withdrawal time in the hot plate test, suggesting the normalization of pain behavioral alteration in CCI-subjected rats **(Figure 3).**

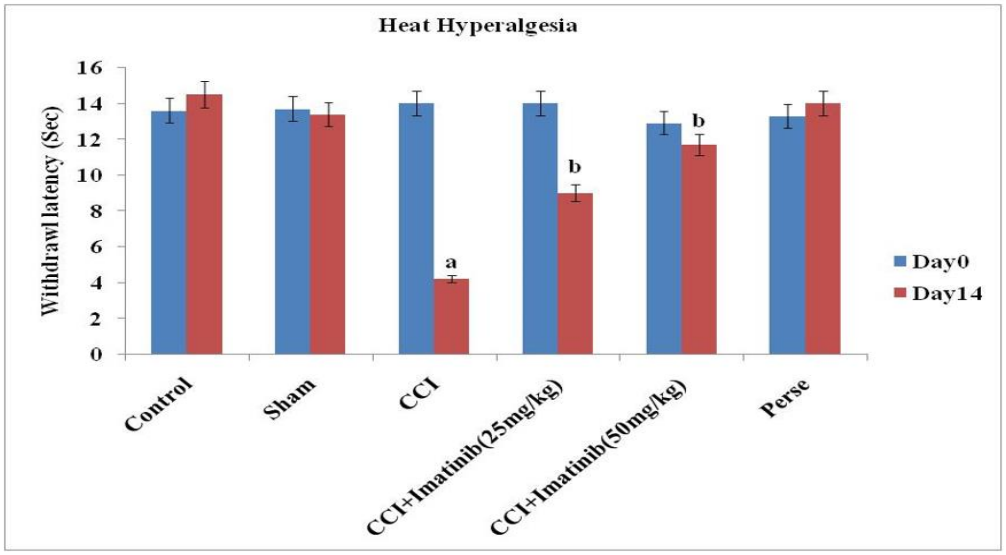

Figure 1: Effect of pharmacological interventions on chronic constriction injury-induced heat hyperalgesia assessed by hot plate test. Values are expressed as mean ± S.D., n=5 rats per group; Two- way ANOVA followed by Bonferonni 's post hoc test. $^{a}p< 0.05$ vs sham control, $^{b}p<0.05$ vs chronic constriction injury

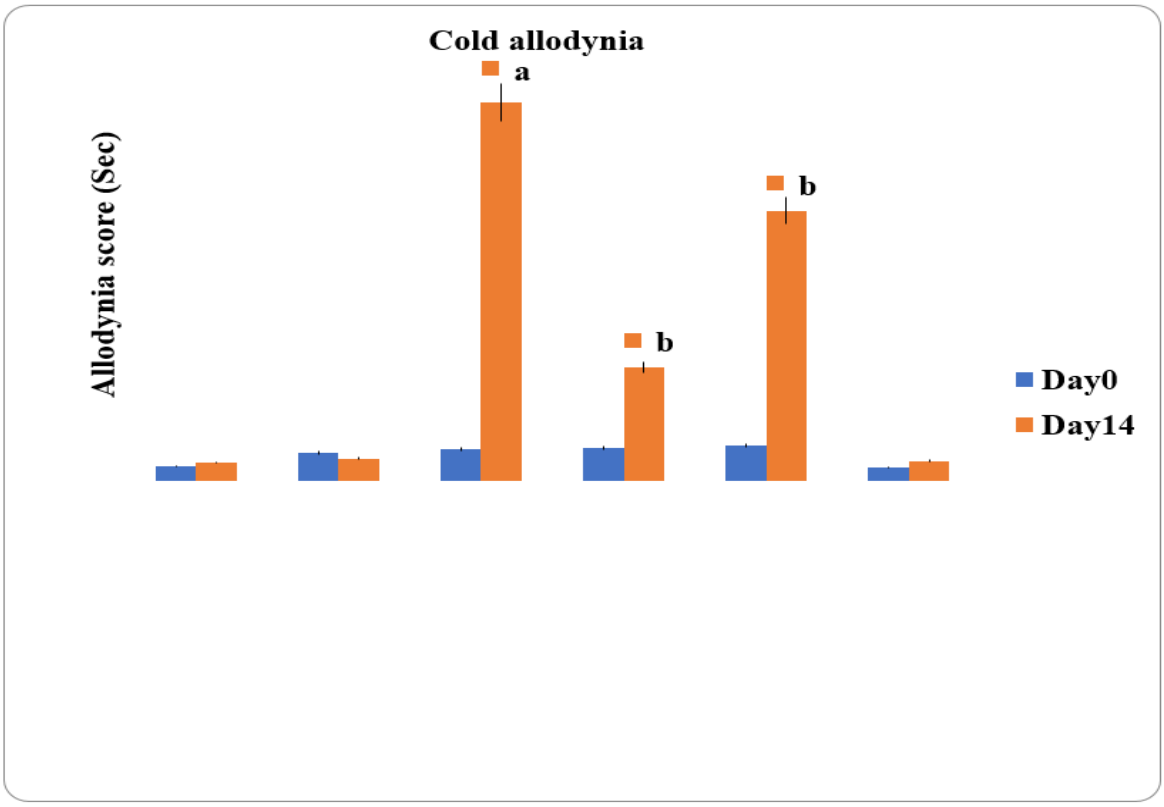

Figure 2: Effect of pharmacological interventions on chronic constriction injury-induced paw cold allodynia assessed by acetone drop test. Values are expressed as mean ± S.D., n=5 rats per group; Two- way ANOVA followed by Bonferonni 's post hoc test. [a]$p< 0.05$ vs sham control, [b]$p<0.05$ vs chronic constriction injury

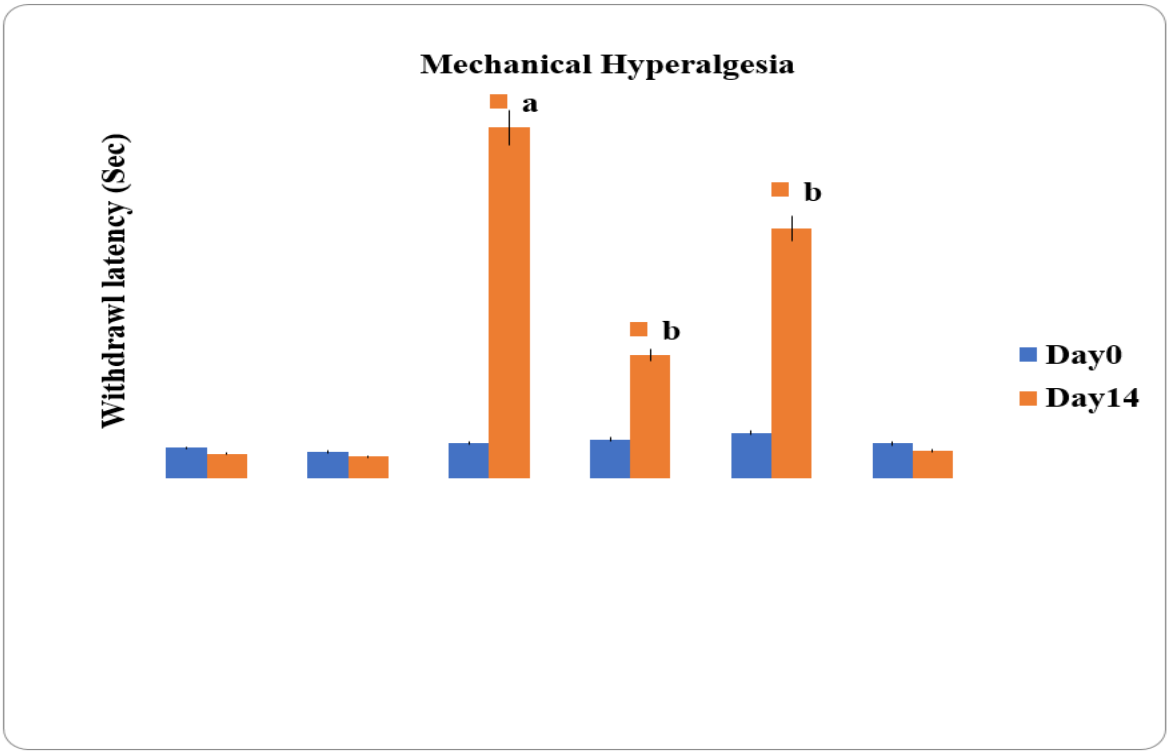

Figure 3: Effect of pharmacological interventions on chronic constriction injury-induced Values are expressed as mean ± S.D., n=5 rats per group; Two- way ANOVA followed by Bonferonni 's post hoc test. [a]$p< 0.05$ vs sham control, [b]$p<0.05$ vs chronic constriction injury

Imatinib is a 2-phenyl amino pyrimidine derivative and is widely employed as an anti-cancer drug, preferably in chronic myeloid leukemia and gastrointestinal stromal tumor [13, 14]. There have been studies showing the relationship between tyrosine kinase and neuropathic pain [43, 44]. Imatinib mesylate is a selective protein tyrosine kinase inhibitor, which can inhibit PDGF-R, BCR/Abl, c-KIT, c-fms, TCR/Abl, Lck, FLT-3 and MAPKs activities on the various cell types [12]. It has also been demonstrated that TrkA expressed on the nociceptors are directly involved in nerve growth factor-induced hyperalgesia [20]. A study by Tender et al has shown that tyrosine kinase C has modulatory effect on neuropathic pain [44]. It has also been demonstrated PDGFR-β is located on the myelinated and non-myelinated nerves, dorsal root ganglion neurons and the spinal dorsal horn [45-47]. Further, PDGFR-β inhibition has also been shown to potentially reverse the already established allodynia and significantly enhance the effectiveness of morphine in neuropathic pain-subjected animals [48]. Considering the evidence of tyrosine kinases in neuropathic pain, it can be plausible to suggest that imatinib might have shown its beneficial effects in CCI-induced neuropathic pain through tyrosine kinase inhibition **(Figure 4)**.

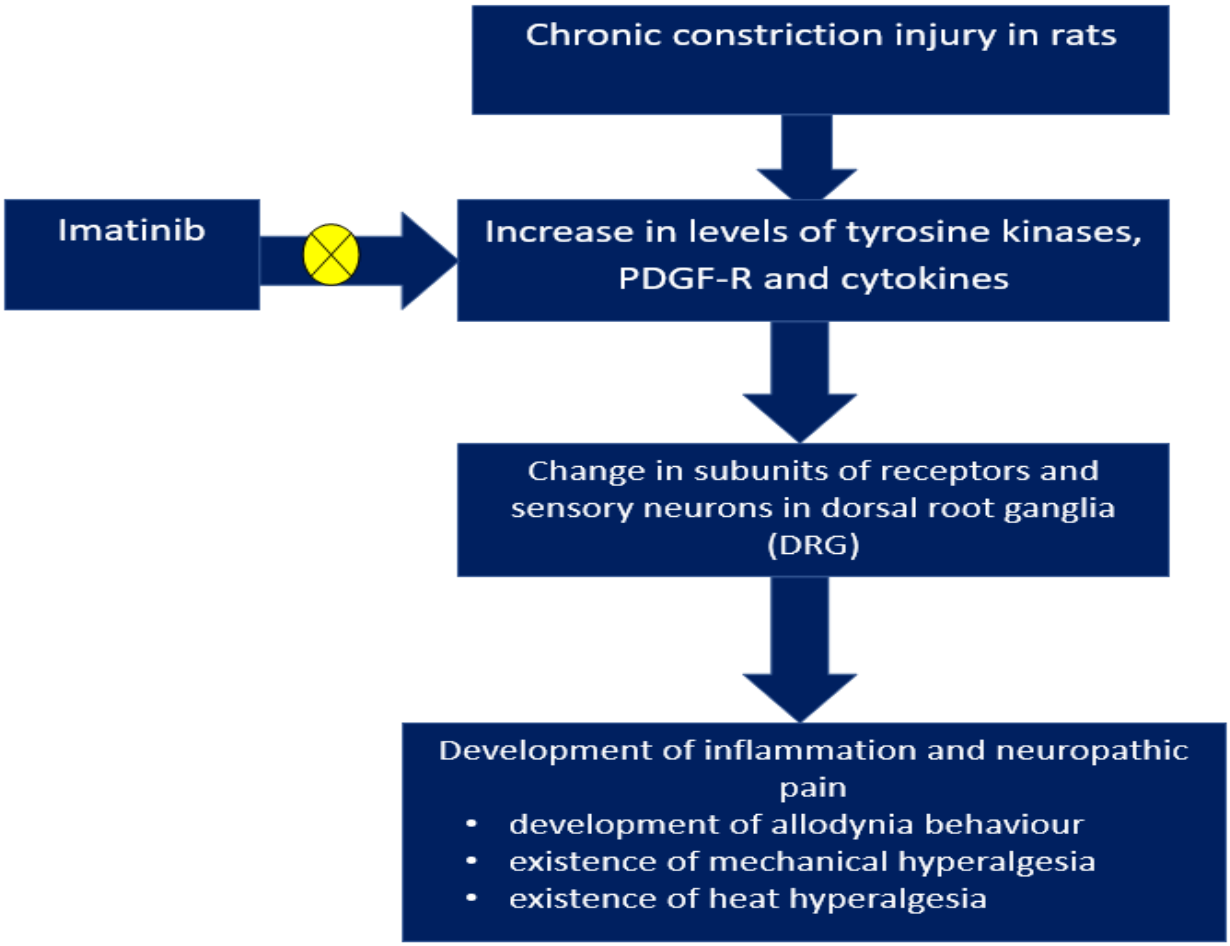

Figure 4: Summarized effects and possible mechanisms of imatinib in CCI-subjected rats

To best of our knowledge, it is the first research study depicting the pain attenuating potential of imatinib in neuropathic pain. Nevertheless, future studies are required to establish the pain attenuating potential of imatinib in other pain models and to delineate the signaling cascade involved in attenuating pain mechanisms of imatinib.

The authors have no conflict of interest

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