Original Article

Effect Of Metabotropic Glutamate 5 Receptor Antagonists Modulator In Rats With Neuropathic Pain

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Abstract

The modulation of experimental induceded antinociception and antihyperalgesia is mediated by the metabotropic glutamate 5 (mGlu5) receptor, which is also involved in neuropathic pain. Multiple pain models benefit from the antihyperalgesic effects of systemic mGlu5 receptor antagonists (R,S)-alpha-2-methyl-4sulphonophenylglycine (MSPG). In rats with chronic neuropathic pain, the purpose of this study is to assess the effects of systemic and intrathecal (MSPG) treatment. Rats were used to create a neuropathic pain model by spinal nerve ligation (SNL) at L5–6 and CCI. Behavior tests were used, including the Von Frey and the hot water tail flick tests. On both acute and chronic pain, the effects of low, medium, and high doses of MSPG were investigated. In the Von Frey tests but not the tail flick tests, systemic and intrathecal MSPG both demonstrated dose-dependent antiallodynic effects. The antinociceptive effect in the latter test was actually diminished by high dosages of MSPG. Low dosages of MSPG reduced morphine tolerance in both tests following chronic intrathecal co-administration of MSPG. Only MSPG reduced neuropathic pain systemically, and only in the Von Frey tests—not the tail flick tests—and MSPG had no impact on morphine tolerance in either test. Using mGlu5 receptor antagonists therapeutically may have diverse outcomes in various pain models.

Keywords: NMDA receptor; Rat brain; mGluR1; mGluR5.

1. Introduction

Numerous studies on the antihyperalgesic effects of metabotropic glutamate receptors, in particular subtype 5 receptor, have been conducted in a variety of pain models, including acute and chronic pain including cancer pain, neuropathic pain, visceral pain, and inflammatory pain. MPEP, SIB-1893, and SIB-1757, three noncompetitive mGlu5 receptor antagonists, are currently being employed as effective tools to investigate how endogenous activation of Neurodegeneration and overall neuronal function are impacted by mGlu5 receptors. The metabotropic glutamate 5 (mGlu5) receptor participates in the control of m-opioid-induced antinociception and antihyperalgesia as well as the processing of pain (1,2). The antihyperalgesic effects of the systemic mGlu5 receptor antagonists 2-methyl-6-phenylethynylpyridine (MPEP) and 3-[(2-methyl-1,3-thiazol-4-yl) ethynyl] pyridine (MTEP) is seen in a variety of pain models, but few research have examined their interactions with morphine.in models of neuropathic pain (3,4). This study's objective is to find the results of (MSPG) reduced the intensity of these pains when administered systemically, intrathecal administration of MSPG had an antihyperalgesic effect in models of neuropathic pain. Research on the effects of mGlu5 receptor antagonists on neuropathic pain effects in rats (5,6).

2. Materials and methods

2.1. Care for animals

On 25 Wistar rats, the experiments were conducted (150–250 g). The trials were carried out in compliance with the regulations set forth by the institution's animal welfare committees. A 12–12 h light–dark cycle was used for the animal housing process, which was conducted at 23 2 °C, 50 1% relative humidity, and 23 2 °C. Animal care committee approval and compliance with CPCSEA criteria were obtained for experiments involving animals at the School of Pharmacy, Bharat Institutional of Technology Meerut. Before the trial, rats had a 3-day adaptation period. To the randomization and treatments, all investigators were concealed. 06 animals total—three males and three females—were divided equally among each group.

2.2. Experimental Procedures

The 50% paw withdrawal threshold (PWT) was established utilizing the previously stated up-down approach to assess the behavioral response to mechanical stimulation (7–9). Rats were placed in separate plexiglass boxes on a stainless-steel mesh floor and given at least 20 minutes to get used to their new environment. The plantar surface of a hind paw was subjected to a series of calibrated Von Frey monofilaments that were applied perpendicularly and bent for six seconds. Positive reactions were interpreted as quick withdrawals or paw flinching. mGlu5 receptor antagonists as well as to observe their effects (10,11).

2.3. Drugs and Administration

By intrathecal injection, 10% dimethyl sulfoxide (DMSO) served as the vehicle control while mGlu5 receptor antagonist (R,S)-alpha-2-methyl-4sulphonophenylglycine (MSPG) was used as the antagonist. Drugs were delivered by SC and IT routes after being dissolved in 0.9% saline for the study. On the seventh day following surgery, all medications were started to be administered. A single MSPG dosage was done 30 minutes prior to the saline injection. Following a medication or saline injection, behaviour assessments were conducted 30 minutes later. At 1, 7, 14, 21, and 28 days, behaviour tests were conducted. Behavior tests were conducted every day 30 minutes following the morning therapy. Saline was administered to the control group on the same schedule. Sevoflurane was used to induce and maintain the animals' anaesthesia. Drugs (10,100 g) were then delivered intratracheally at the lumbar 4-5 level using 30-G needles (12).

2.3. Paclitaxel-Induced Neuropathic Pain Model

In a nutshell, paclitaxel was dissolved in a 1:1 (w/v) solution of 0.9% NaCl (normal saline) and 0.2 mg/ml just before administration. Normal saline comprising roughly 1.7% of dosage per dose served as the control substance. Every day, the mice received intraperitoneal (i.p.) injections of paclitaxel (4 mg/kg) or a vehicle control.

3. Psychological Tests

The use of mechanical stimuli, a heat test, and conditioned place preference (CPP) was conducted in accordance with previously published methods (12–15) Animals were taught for three days, spending an hour a day using the testing equipment, to determine baseline threshold and latency. Baseline testing was conducted one day before the introduction of the drug. The two tests were separated by one hour. All behavioural assays were conducted by a single researcher who was blind to all treatments (16).

In response to mechanical stimulation, paw withdrawal frequency (PWF) was initially determined. On the plantar surface of the right hind paws, a 0.4-g von Frey filament was placed. The number of paw withdrawals in response to stimulation was provided as a percent response frequency [(number of paw withdrawals/10 trials) 100]. Stimulations were carried out ten times.

Rodents were separately put in Plexiglass chambers on glass plates and their paw withdrawal latency (PWL), which measures heat sensitivity, was measured by activating the plantar centre with a laser beam. The PWL was calculated as the interval between the initiation of the light beam and the foot withdrawal. In order to prevent tissue damage, tests were run five times at 5-min intervals for a maximum of 20 s.

3.1. Paw Withdrawal Latency (PWL)

Effects of MSPG on paw withdrawal threshold (PWT) and paw withdrawal latency (PWL) in rats following chronic constriction injury (CCI/CINP/DNP). The CCI/CINP/DNP model's experimental setup is shown in the top panel for rats. To study the impact of CCI + MSPG, i.p.) on thermal PWL and mechanical PWT evoked by chronic constriction injury, pentobarbital (40 mg/kg) anaesthesia was administered to rats (CCI). The paw pressure test and heat stimulation were used to measure PWL and PWT before (day -1), as well as on days 1, 3, and 7 and 14 after surgery. Data analysis was done using the GraphPad Prism 9 programme. We created box-and-whiskers plots, where each "box" represented the median, 25th and 75th quartiles, and matching "whisker" represented the 5th and 95th percentiles. With the post-hoc Tukey's test for group comparisons, behavioural data were examined using a two-way repeated measures ANOVA. Based on similar behavioural and biochemical tests, the sample size (n = 6) was determined (17,18). A statistically significant difference was shown by the value of P 0.05.

4. Results

4.1. MGlu5 is the DRG's leading indicator of paclitaxel-Induced Neuropathic Pain.

Groups had similar levels of mechanical allodynia and Von Frey heat sensitivity (n= 6) show in **Figures 1 and 2**. As previously mentioned (19), rats who received paclitaxel intraperitoneally but not the vehicle had thermal hyperalgesia and persistent pain hypersensitivity (markedly elevated PWF after stimulation with a 0.4 g von Frey filament). These side effects began 3 days after the initial paclitaxel therapy and persisted for three weeks or longer (20,21). The behaviour and protein levels in DRG specimens were also time-dependently increased by paclitaxel administration. In comparison to animals that received a vehicle injection, the change in L3-5 DRGs was greater on days 3, 7, 14, 21 and 28 following the initial administration of paclitaxel. Accordingly, on days 3, 7, 14, 21, and 28 compared to the vehicle group, mGluR5 protein levels in L3-5 DRGs rose. As anticipated, the vehicle had no effect on the amount of mGluR5 protein and mRNA in the DRGs at rest. The aforementioned research showed that paclitaxel injection enhanced persistent DRG mGluR5 expression, which may be important for the PINP's initiation and maintenance (22–24).

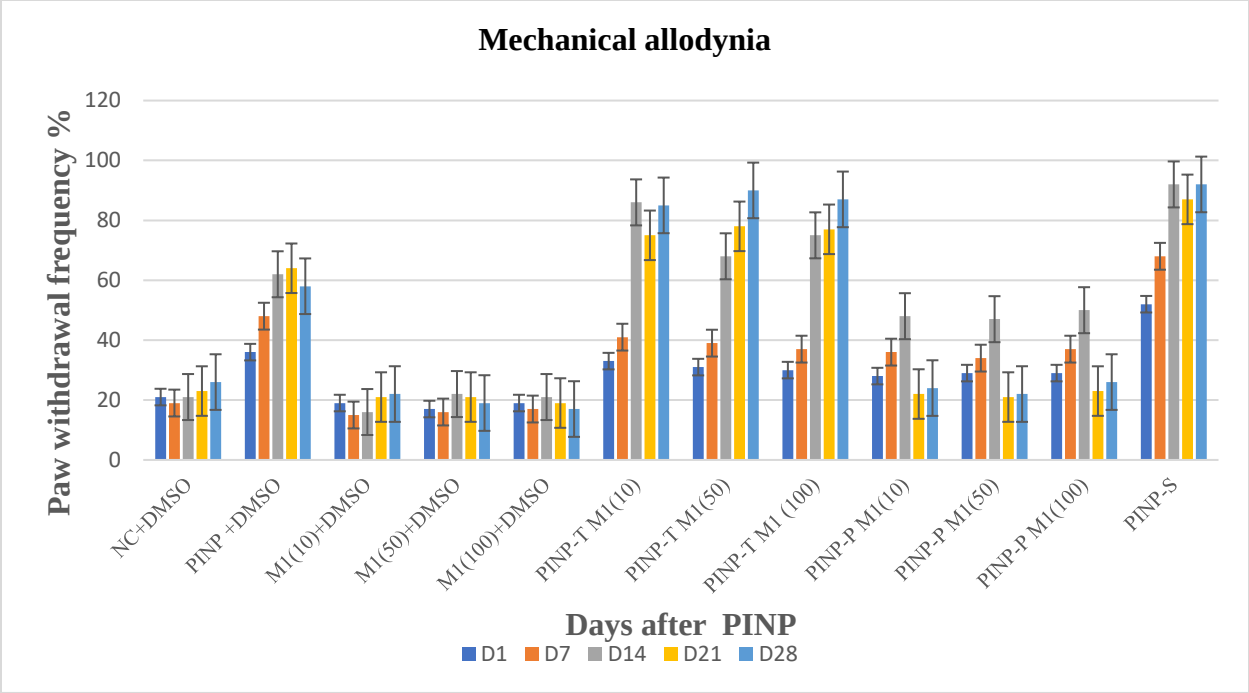


Fig:1 Effects of MSPG on paw withdrawal latency (PWL) and paw withdrawal threshold (PWT) Mechanical allodynia evoked by Paclitaxel-Induced Neuropathic Pain (PINP) in rats.

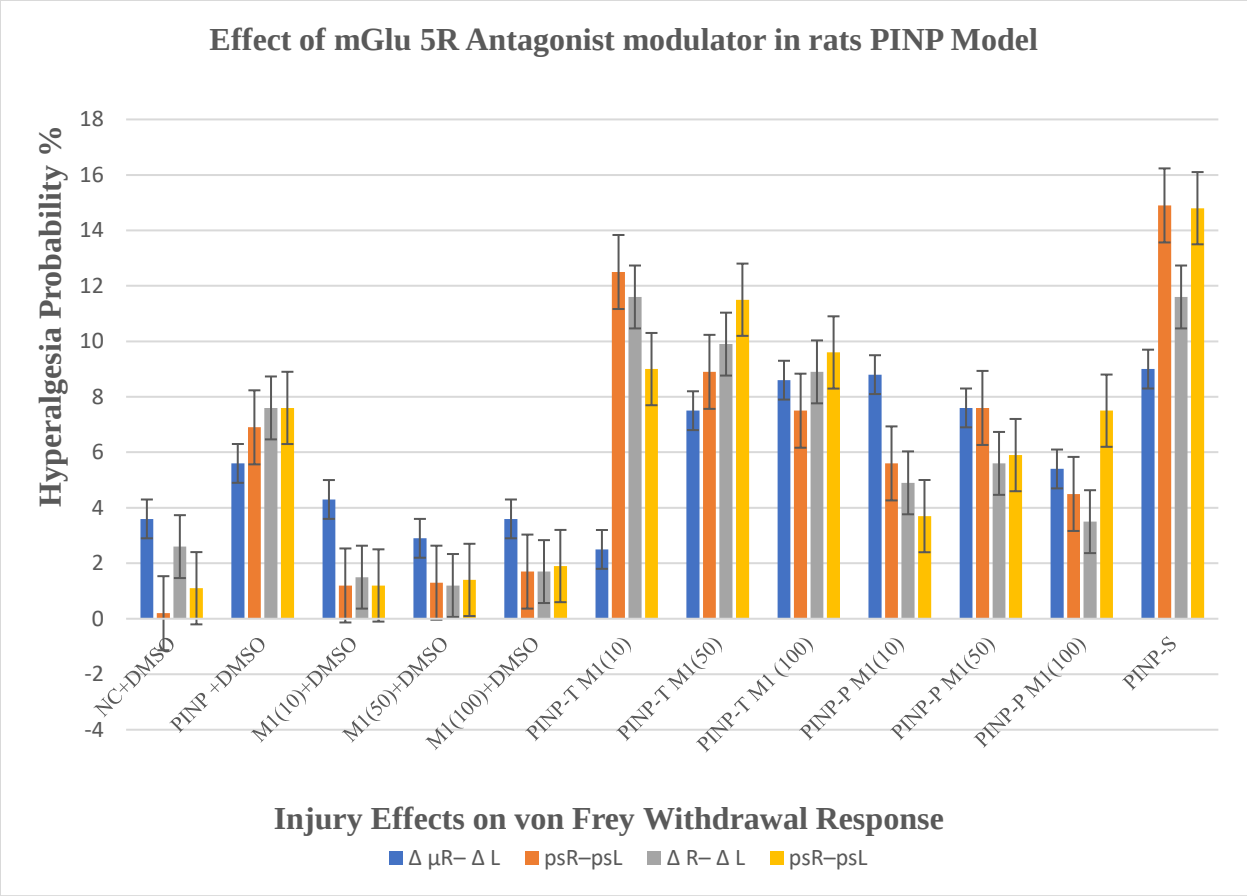
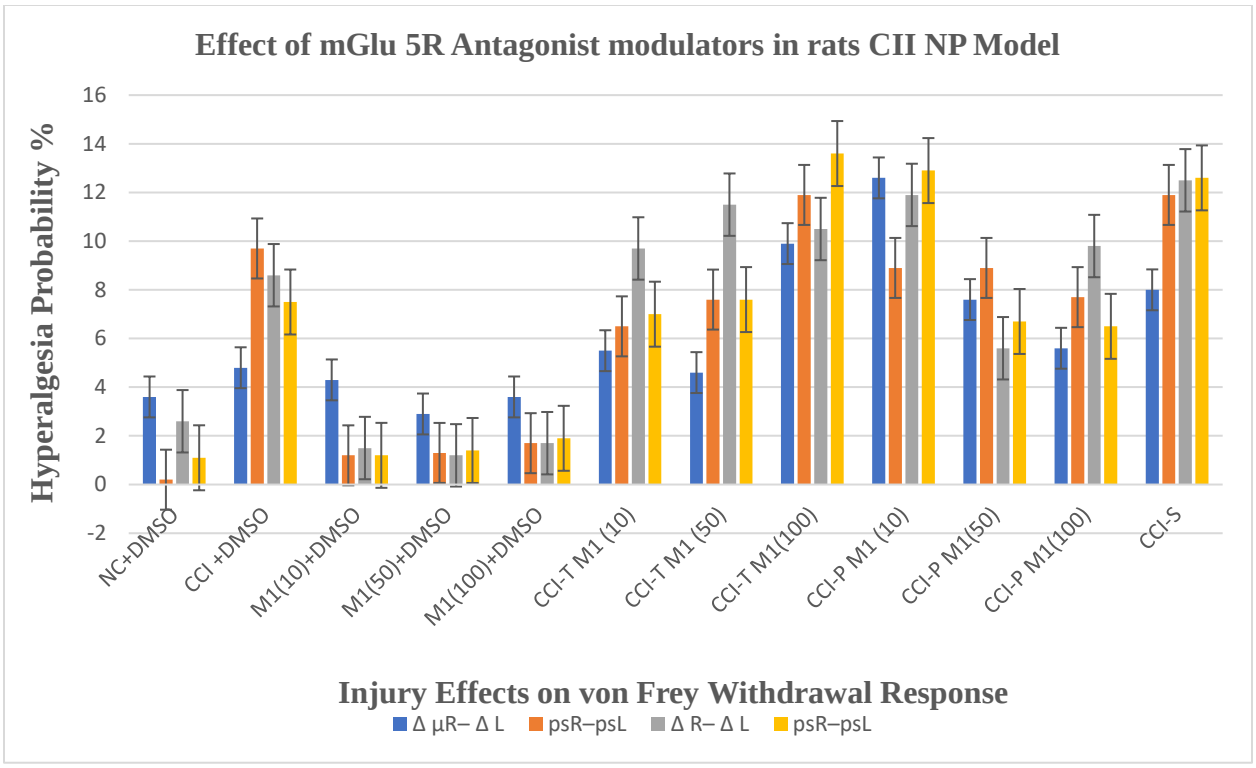


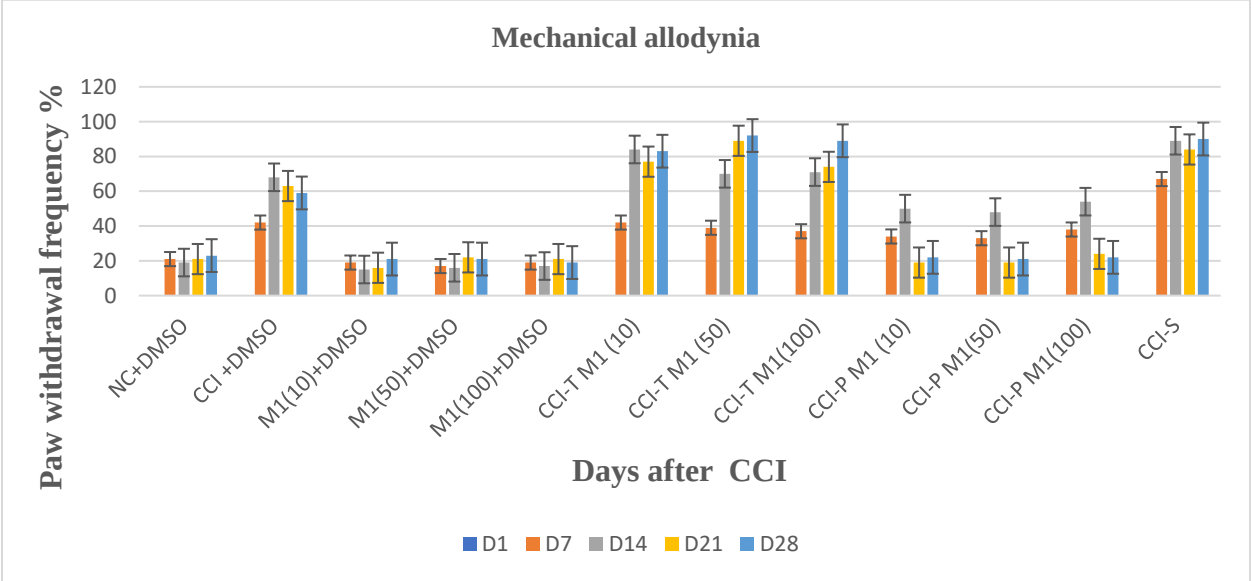
Fig:2 Effects of MSPG on paw withdrawal latency (PWL) and paw withdrawal threshold (PWT) Von Frey evoked by Paclitaxel-Induced Neuropathic Pain (PINP) in rats.

4.2 Chronic constriction injury (CCI) Neuropathic Pain is accompanied mGlu5 in DRG

Mechanical allodynia and Von Frey heat sensitivity were comparable in both groups (n = 6) **Figures: 3, Figures:4**. Effects of MSPG on paw withdrawal latency (PWL) and paw withdrawal threshold (PWT) evoked by chronic constriction injury (CCI) in rats. The top panel depicts the experimental design for the CCI model in rats. Rats were anesthetized with pentobarbital (40 mg/kg) for CCI surgery (day 0) to determine the effect of CCI + MSPG, i.p.) on thermal PWL and mechanical PWT evoked by chronic constriction injury (CCI). PWL and PWT were estimated by the thermal stimulation and paw pressure test, respectively, applied before (day -1) and on days 1, 3, 7, 14, 21, 28 after surgery.



Figures 3: Effects of MSPG on paw withdrawal latency (PWL) and paw withdrawal threshold (PWT) Von Frey evoked by chronic constriction injury (CCI) in rats.

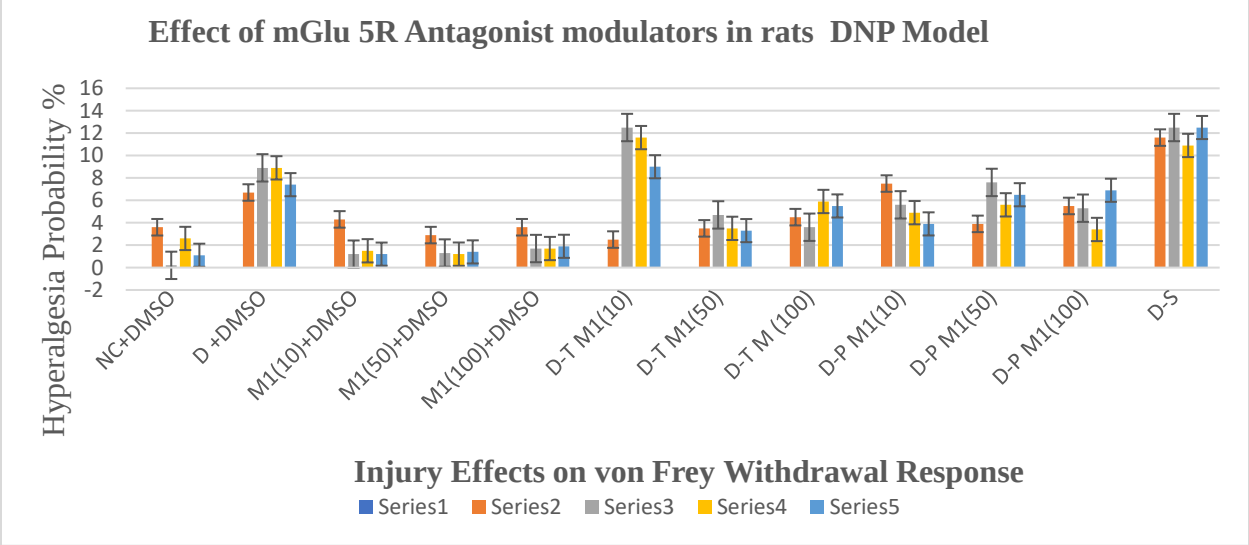


Figures 4: Effects of MSPG on paw withdrawal latency (PWL) and paw withdrawal threshold (PWT) Mechanical allodynia evoked by chronic constriction injury (CCI) Pain in rats.

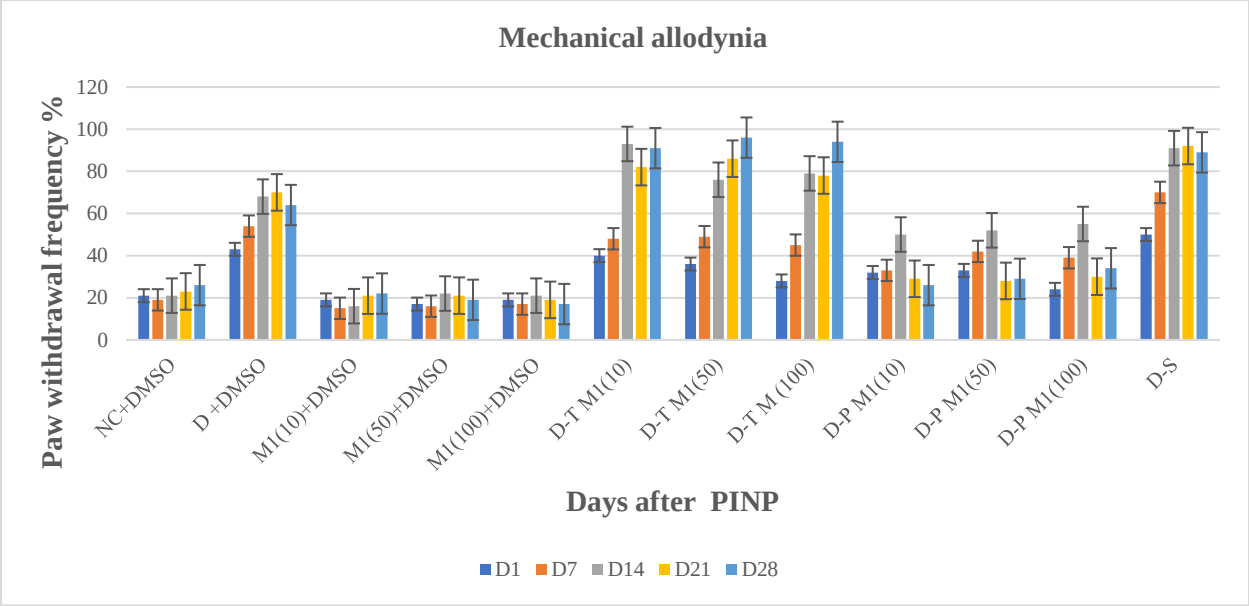
Sham-operated (Sham) rats were subjected to the same surgical procedure, without manipulation of the nerve. Data represent the mean ± SEM for 6 rats per group. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, and $^{\#\#\#}p < 0.001$ compared to the sham group; $^{*}p < 0.05$ and $^{**}p < 0.01$ compared to the CCI group.

4.3. Disease-Induced Neuropathic Pain is accompanied mGlu5 Antagonist in DRG

Basal Mechanical allodynia and Von Frey heat sensitivity were comparable in both groups (n = 6) **Figures: 5, Figures:6**. Effects of mGlu5 Antagonist modulators on paw withdrawal latency (PWL) and paw withdrawal threshold (PWT) evoked by diabetic neuropathy. Streptozotocin (STZ)-induced diabetes in the rat has been increasingly used as a model of painful diabetic neuropathy and to assess the efficacies of mGlu 5R antagonist of potential analgesic agents in neuropathic pain. in rats. The top panel depicts the experimental design for to determine the effect of mGlu in Disease-Induced Neuropathic Pain on thermal PWL and mechanical PWT. PWL and PWT were estimated by the thermal stimulation and paw pressure test, respectively, applied before (day -1) and on days 1, 3, 7, 14, 21, 28 after surgery.



Figures 5: Effects of MSPG on paw withdrawal latency (PWL) and paw withdrawal threshold (PWT) Von Frey evoked by Disease-Induced Neuropathic Pain in rats.



Figures 6: Effects of MSPG on paw withdrawal latency (PWL) and paw withdrawal threshold (PWT) Mechanical allodynia evoked by Disease-Induced Neuropathic Pain in rats.

4.4. PINP Is Blunted by Intrathecal MSPG Administration

Intrathecal administration of MSPG (10,50 and 100) was done ten minutes prior to each paclitaxel injection in order to evaluate its specific impact on PINP. First, when compared to regular saline, MSPG had no overt impact on peripheral mechanical and heat sensitivity. It's interesting to note that mice pretreated with MSPG at doses of 10 and 100 mg, but not 1 mg, had lessened the mechanical and thermal allodynia and hyperalgesia caused by paclitaxel, as seen by noticeably reduced PWF control and noticeably increased PWL in the treatment groups. The dose-dependent anti-hyperalgesic effects of MSPG became apparent three days after the initial paclitaxel injection and persisted for 28 days.

4.5. MSPG Inhibits (4.5) Upregulation of mGluR5 by Paclitaxel in DRGs

The quantity of DRG mGluR5 was measured following paclitaxel exposure to determine whether mGluR5 plays a role in the anti-nociceptive impact of MSPG. Unexpectedly, MSPG pretreatment decreased DRG mGluR5 upregulation. According to the aforementioned research, mGluR5 downregulation caused MSPG to impair PINP production and maintenance.

4.6. Inhibition of mGluR5 Lowers PINP

Mice were given intrathecal injections of MSPG (mGluR5 antagonist; 1, 10, or 100 nmol) 10 min before each injection of paclitaxel to validate mGluR5's role in transducing nociception in PINP. As expected, behavioural assays demonstrated that paclitaxel-treated mice had significantly increased paw withdrawal mechanical threshold and thermal latency, indicating that mechanical allodynia and thermal hyperalgesia were robustly and dose-dependently reversed by MSPG at 10 and 100 nmol, but not 1 nmol.

4.7. Blending MSPG in the PINP

Following that, von Frey and hot plate assays showed that MSPG (10, 50,100) and MPEP (1 nmol) at subthreshold doses had no impact when given alone on the paw withdrawal threshold and latency. However, simultaneous

administration of MSPG and MPEP effectively reduced mechanical allodynia and thermal hyperalgesia. The aforementioned results further suggested that mGluR5 was involved in MSPG's anti-PINP activity. In the PINP, MSPG alone has a weaker anti-hyperalgesic action than the combination of the mGluR5 antagonist MPEP and MSPG.

4.8. MSPG's therapeutic effectiveness

Next, it was investigated whether MSPG similarly reduces acute pain brought on by intrathecal administration of the mGluR5 agonist CHPG at 1 nmol. Ten minutes before the CHPG treatment, an intrathecal injection of MSPG (100) was administered. Our findings showed that from 1 to 12 hours after intrathecal dose, CHPG caused acute mechanical allodynia and thermal hyperalgesia in naive rats. It's interesting to note that MSPG medication effectively stopped CHPG-related acute pain. All of the aforementioned information pointed to the critical part played by mGluR5 in anti-nociception brought on by MSPG and chemotherapy-related pain. MSPG Therapy Attenuates Acute Pain Caused by the Metabotropic Glutamate Receptor 5 Agonist 2-Amino-2- (2-Chloro-5-Hydroxyphenyl) Acetic Acid.

4.9. MSPG Controls mGluR5 in DRGs

Ten days after the first dose of paclitaxel was administered, mice's L3-5 DRGs were taken, and the levels of mRNA and membrane protein expression of receptors that are unmistakably linked to pain, such as MOR, NR1, GluA2, and GABAB, were assessed. In paclitaxel + MSPG-treated and paclitaxel + MSPG-treated DRGs, NR1 expression was lowered and GluA2 expression was elevated in comparison to the paclitaxel group.

4.10. MSPG function in Neuroinflammation.

Strong anti-inflammatory properties of MSPG may play a role in PINP's anti-hyperalgesic mechanism. It is currently unknown, nevertheless, whether mGluR5 contributes to the anti-inflammatory action of MSPG. Ten days after the initial paclitaxel therapy, L3-5 DRGs were collected, and chemokines and pro-inflammatory cytokines associated with paclitaxel injection were quantitated. TNF-, IL-1, and IL-6 levels were found to be considerably higher in DRGs treated with paclitaxel, according to our research. As mGluR5 is not implicated in MSPG's anti-inflammatory mechanism, this finding showed that MSPG could lower PINP through an anti-inflammatory mechanism (25,26).

5. Discussion

The inhibition of mGluR5 activation and neuroinflammation by MSPG in the prevention and treatment of PINP was previously unknown, according to this study. From day 3 through at least 28 days following paclitaxel injection, the animals had mechanical allodynia, thermal pain, and spontaneous pain. These symptoms were accompanied by elevated levels of mGluR5, chemokines, and pro-inflammatory substances in DRGs.

A rising number of studies have shown how the development of various neuropsychiatric illnesses is influenced by mGluR5-induced central nervous system (CNS) neurodegeneration. More recently, it has been demonstrated that neurotrauma and peripheral inflammatory reactions activate mGluR5 at excitatory nociceptive synapses, causing chronic neuropathic allodynia and acute inflammatory pain (27,28)

Additionally, animal models are used to control mGluR5-dependent synaptic plasticity in opioid-triggered analgesic tolerance. Here, we describe the mGluR5 expression of mice given paclitaxel for the first time, which supports the progression of the PINP phenotype. The aforementioned data strongly suggests that DRG mGluR5 activation contributes to the pathophysiological process of PINP. However, more research is needed to determine how mGluR5 regulates DRG nociception following paclitaxel treatment.

NMDAR and AMPAR are also co-expressed in neural synapses in addition to mGluR5 (29,30). It is possible that mGluR5 is involved in neuropathic pain because it alters the expression of glutamate receptors in neurons, specifically NMDA (31–33) and AMPA (34) receptors. Presynaptic mGluR5 activity in the spine is increased in paclitaxel-induced neuropathy, acting as an upstream signal for PKC-induced tonic NMDAR induction (35,36). Presynaptic NMDARs are tonically activated by chemotherapy, which encourages glutamate release at synapses in the spinal dorsal horn

(36). Ketamine medication can thereby dramatically ease PINP and lower opioid usage (37). When mGluR5 is activated, neurons produce more NR1 and internalise more GluA2 (38), which results in more NMDAR- and AMPAR-mediated neuronal excitatory afferents. In the situation of spinal nerve ligation neuropathic pain, MOR expression is reduced (39). MMG22, a dual-acting MOR agonist and mGluR5 antagonist, shows strong anti-hyperalgesic effects, especially in the pain associated with cancer, inflammatory pain, and neuropathic pain (40–44). The CNS's major regulators of fast synaptic inhibition are GABAARs (45).

Mechanical allodynia, aberrant neural responses, and dysregulated pro- and anti-inflammatory factors in the spinal dorsal horn are all components of chemotherapy-induced peripheral neurotoxicity (CIPN) (46,47). One of the most important factors in the development of paclitaxel-mediated neuropathic pain is neuroinflammation (48). Strong anti-inflammatory, antioxidant, and neuroprotective properties are demonstrated by MSPG and its derivatives. When BV2 cells are exposed to LPS, artemisinin decreases NO secretion and significantly reduces IL-1, IL-6, and TNF- levels (49).

This study showed that MSPG had excellent therapeutic effects on chemotherapy-related pain and neuropathy. It is important to note that MSPG is inexpensive, low-toxic, and very effective, all of which may contribute to the therapeutic alleviation of CINP. MSPG remarkably crosses the blood-brain barrier effectively (50). MSPG may be well suited for concurrent usage with other chemotherapeutic medicines to avoid the development of chemotherapy pain because it exhibits regulatory effects on several pain-related ion channels, anti-neuroinflammatory activity, and anti-cancer capabilities (51). Chronic inflammation that results from nerve damage fuels the development and maintenance of neuropathic pain. Through their hydrolytic action, inflammatory mediators including secreted phospholipase A2 (sPLA2) control nociceptive and excitatory neural transmission at the onset of pain (52,53). It was shown that the pro-inflammatory mediators in the dorsal root ganglion (DRG) increased in the chemotherapy pain model, indicating the production of neuroinflammation in the DRG. It is generally recognised that trigeminal neuralgia is caused by neuroinflammation in glial cells, which increases presynaptic glutamate release and activates postsynaptic mGluR5 (53,54). An important objective in the management of persistent neuropathic pain should be to balance glutamate release and absorption after nerve injury (55,56). We speculate that neuroinflammation may lead to the release of glutamate, which activates mGluR5, in the pathogenesis of chronic pain. MSPG exerts positive anti-inflammatory effects to reduce the activation of mGluR5, which further results in anti-inflammatory and analgesic effects. This study did not monitor glutamate levels within the DRG, which is one of our limitations.

Additionally, we discovered a really intriguing phenomenon: MSPG significantly increased levels of Myelin Protein Zero (MPZ) (data not shown). Simple MSPG administration could greatly increase MPZ expression. Since MPZ is a crucial protein in Schwann cells and is essential for the production of myelin and the maintenance of proper morphology, it is thought that MSPG greatly upregulates MPZ in DRG (57–59). Additionally, demyelination plays a significant role in the neuropathy caused by paclitaxel (60).

The bottom line is that MSGP can successfully prevent and treat PINP, possibly by preventing mGluR5-related neuroplasticity and lowering neuroinflammation. According to the current findings, MSPG represents a cutting-edge treatment option for neuropathic pain following chemotherapy.

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