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Research Article
Effects of Sumatriptan, Baclofen and Gabapentin on Acute and Chronic Neuropathic Pain in a Rat Model of Sciatic Nerve Ligation

[1,2]Bader Ahmad Algohane, [1,3]Hussein Mohammad Ali, [1]Ahmad Hamad Alhowail, [1,4]Mohammed Fulayyih Alharbi and [1,5]Hossam Abdelkader Elsisi

[1]Department of Pharmacology and Toxicology, College of Pharmacy, Qassim University, Buraydah 51452, Saudi Arabia
[2]Ohud Hospital, Alsalam, 42354 Al-Madinah Al-Munawara, Saudi Arabia
[3]Department of Biochemistry, Faculty of Medicine, Al-Azhar University, Assiut 71524, Egypt
[4]Buraydah Central Hospital, AL Taalim, Buraydah 52361, Qassim, Saudi Arabia
[5]Department of Clinical Pharmacology, Faculty of Medicine, Zagazig University, 44511 Zagazig, Egypt

Abstract

Background and Objective: Neuropathic pain remains a complex and poorly managed condition, with current treatments often associated with significant side effects. This study aims to evaluate and compare the effects of sumatriptan, baclofen and gabapentin on acute and chronic pain, focusing on their impact on neurotransmitters and neuropeptides. **Materials and Methods:** Acute and chronic pain models were evaluated in rats using the plantar analgesia meter, formalin test and sciatic nerve ligation (CCI) model. Drugs were administered intraperitoneally and pain responses were measured at 30, 60 and 90 min post-treatment. Biomarker analysis was conducted using ELISA to measure GABA, glutamate, substance P (SP) and Calcitonin Gene-Related Peptide (CGRP) levels in brain tissue. Statistical analysis was performed using GraphPad Prism® version 8, with significant differences determined by one-way ANOVA followed by Tukey's *post hoc* test for multiple comparisons ($p<0.05$). **Results:** In the acute pain model, no significant differences were observed between treatments. In the CCI model, gabapentin (GBP) produced the most significant reduction in pain, particularly at 30 and 60 min. The formalin test showed that GBP significantly reduced paw licking time during both acute and chronic phases compared to baclofen (BAC), sumatriptan (SUM) and control groups. Additionally, GBP and BAC increased GABA levels, while GBP and SUM reduced SP and CGRP levels. Glutamate levels remained unchanged across all groups. **Conclusion:** Gabapentin was the most effective in pain models, influencing key brain biomarkers, while baclofen and sumatriptan showed moderate effects.

Key words: Neuropathic pain, acute pain, chronic pain, sumatriptan, baclofen, gabapentin

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Corresponding Author: Hossam Abdelkader Elsisi, Department of Pharmacology and Toxicology, College of Pharmacy, Qassim University, Buraydah 51452, Saudi Arabia

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Neuropathic pain is a complex and debilitating condition that arises from injury or dysfunction within the somatosensory system. Over the years, extensive research has contributed to our understanding of neuropathic pain, leading to the identification of various underlying aetiologies and distinct pain phenotypes. This type of pain is often classified according to its cause, such as diabetes, infections like herpes zoster, nerve compression or damage, channelopathies and autoimmune disorders[1]. The processes that drive neuropathic pain are diverse, but a common feature is the involvement of abnormal signaling in the nervous system. Key neurotransmitters, such as GABA (Gamma-Aminobutyric Acid) and glutamate, play crucial roles in modulating pain perception by maintaining the balance between excitatory and inhibitory signals within the nervous system[2]. Additionally, neuropeptides like (SP) (CGRP) are integral to the development of pain and hyperalgesia, significantly influencing pain sensitivity and perception[3].

Despite the availability of various pharmacological approaches for managing neuropathic pain, including opioids, antidepressants and antiepileptics, pain remains inadequately treated in many patients. These treatments, while effective for some individuals, often come with significant adverse effects, such as sedation, cognitive impairment, dependence or gastrointestinal issues. This highlights the need for more effective and safer therapeutic options that can provide relief without the side effects commonly associated with current treatments.

Sumatriptan, a selective 5-HT1B and 5-HT1D receptor agonist, is primarily used for treating migraines, but it showed effectiveness in some neuropathic pain models[4-6]. Baclofen, a GABA agonist, acts on presynaptic GABA-B receptors to induce hyperpolarization of motor horn cells, providing relief in various pain conditions[7]. Gabapentin, originally developed as an anticonvulsant, is now considered a first-line treatment option for neuropathic pain. Selectively interacts with the α2δ-1 subunit of voltage-gated calcium channels, modulating neurotransmitter release and reducing pain[8]. This study aims to evaluate and compare the effects of baclofen and sumatriptan in different pain models, including acute nociceptive and chronic neuropathic pain and compare their efficacy to the traditional drug gabapentin. Additionally, the study seeks to investigate neurotransmitter and neuropeptide levels in brain tissue samples to clarify the specific mechanisms underlying the pain-modulating effects of these drugs.

MATERIALS AND METHODS

Study area: The study was conducted from November, 2024 to January, 2025 at the Pharmacology Laboratory in the College of Pharmacy, Qassim University, Saudi Arabia.

Drugs and chemicals: Thiopental sodium injection (500 mg) was obtained from Rotexmedica (HAM, DE). Formalin (5% solution) was sourced from Morphisto (FRA, DE). Sumatriptan tablets (50 mg) were acquired from GSK (BRE, UK). Baclofen tablets (25 mg) were procured from Novartis (BAS, CH). Lastly, Gabapentin capsules (300 mg) were obtained from Pfizer (NYC, US). The levels of GABA and glutamate were analyzed using ELISA Kits (MBS269152 and MBS756400, respectively) from MyBioSources (SD, CA, US). Substance P was quantified using an ELISA Kit (E-EL-0067) from Elabscience (HOU, TX, US) and CGRP was measured with an ELISA Kit (BSKR62499) from Bioss Antibodies (WOB, MA, US).

Experimental animals: The study used 108 adult male Sprague Dawley rats, each aged around three months and weighing between 150 and 250 g. The rats were housed in a controlled environment with a temperature of less than 25°C and relative humidity levels around 60%. The rats were randomly divided into four groups (n = 6) for acute pain evaluation; four groups (n = 6) for the formalin test; six groups (n = 6) for chronic pain evaluation and four groups for biomarkers evaluation.

Ethical approval: The study received ethical approval from Qassim University's Ethics Committee (Approval Number 24-14-07).

Plantar analgesic meter: Thermal hyperalgesia was evaluated by measuring the latency of hind paw withdrawal latency by the plantar testing device (Model 7360, Ugo Basile, Comerio, Italy). The animals were randomly divided into four groups as follows: Group I (Control) was administered normal saline (10 mL/kg, i.p.); Group II was given gabapentin (300 mg/kg, i.p.); Group III was treated with baclofen (4 mg/kg, i.p.) and Group IV was administered sumatriptan (4 mg/kg, i.p.). The time of reaction was recorded at 30, 60 and 90 min post-administration using the Plantar Test Analgesic Meter. The mean withdrawal latency for the left hind paw was determined as the mean of two trials, with a 5 min separation between them to avoid thermal sensitization. To prevent tissue injury, a 20 sec cutoff time was used.

Formalin test: Subcutaneous injection of 50 µL of 5% formalin solution was administered into the hind paw of rats using an insulin syringe[9]. The formalin test consists of two phases: An acute phase (0-10 min) and a chronic phase (20-40 min). Nociception was assessed by recording the paw-licking time during these two phases. Rats were randomly divided into four groups, all of which received an intraperitoneal (i.p.) injection; Group I: A control group, which received 10 mL/kg; Group II: A GPB group, treated with 300 mg/kg; Group III: A BAC group, treated with 4 mg/kg and Group IV: A SUM group, treated with 4 mg/kg.

Sciatic nerve ligation: The neuropathic pain model was done by surgery performed under general anesthesia using 40 mg/kg of thiopental. The procedure began by shaving the leg and positioning the rat on a heated mat set to 37°C. The rat was positioned chest down and the left hind leg was elevated and fixed at a 90° angle with masking tape around the foot. A small cut was made parallel to the femur, 3-4 mm below and the skin was gently removed from the surrounding tissue. The connective tissue between the muscles was cut using blunt scissors and a retractor was used to expand the opening so that the sciatic nerve could be exposed easily. Forceps and micro-scissors were used to carefully separate around 10 mm of the sciatic nerve from the surrounding tissues. Four ligatures were put 1 mm apart, close to the sciatic trifurcation, making sure they were tight enough to securely attach to the nerve but not too tight to restrict blood flow. After suturing the muscle layer, staples were used to seal the skin and the wound was sterilized with an iodine solution[10]. Rats were divided into six groups: Group I (Control Normal) received saline without surgery; Group II (Sham) underwent all procedures of surgery without ligation; Group III (Control Postoperative) received saline post-ligation. Sciatic nerve-ligated groups included: Group IV (300 mg/kg GBP), Group V (4 mg/kg BAC), Group VI (4 mg/kg SUM). Drug treatments began 15 days post-ligation and reaction times were measured at 30, 60 and 90 min after (i.p.) injection using a Plantar Test Analgesia Meter.

Measurement of biomarkers: Four groups (control and three treatment groups) were injected with normal saline and the three drugs, respectively then sacrificed after 60 min of injection under anesthesia via cervical dislocation. Brain tissues were homogenized in phosphate-buffered saline (PBS) with a pH of 7.4 and then centrifuged at 5000 rpm for 10 min. The resultant supernatant was then collected and kept at -20°C for laboratory analysis.

Laboratory analysis: The GABA level was done by ELISA kit based on manufacturer instructions. It started with preparing sample reagent and standard, then incubating for 90 min at 37°C, then the plate was washed twice; after that, the biotinylated antibody solution was added and incubation continued at 37°C for an additional 60 min. After three more washes, an enzyme working solution was added and incubated at 37°C for 30 min. Then five washes were done, a color reagent solution was introduced and the plate was incubated at 37°C for 30 min. Optical density was determined by ELISA reader plate (Biotech Instruments, Santa Clara, California, USA) at 450 nm and GABA concentration in the samples was done using the standard curve.

For glutamate analysis, ELISA kits were also used, followed by the manufacturer's standard. The microtiter plate test involved coating the wells and adding standards, samples, blanks and conjugates, then followed by incubation at 37°C for an hour. The plate was washed and blotted, Substrate A and B were added and then the plate was incubated for around 15-20 min. Finally, the optical density (O.D.) was measured at 450 nm with an ELISA reader plate and the glutamate concentration was measured through the standard curve.

The substance P ELISA assay involves adding 50 µL of standards, blanks or samples to wells and then adding a biotinylated detection antibody. The wells were washed three times after incubation at 37°C for 45 min. Next, 100 µL of HRP-conjugate is added, incubated for 30 min at 37°C and washed five times. Then, substrate reagent 90 µL was added and incubated at 37°C in the dark for 15 min. The reaction is stopped with 50 µL of stop solution and the OD is measured at 450 nm to calculate substance P concentrations using a standard curve.

For CGRP analysis, 50 µL of standard dilutions, blank and samples are added to wells, then 50 µL of detection reagent A is added. After shaken, sealed and incubated at 37°C for 1 hr, the plate was then washed three times. Next, a reagent b was added, followed by 1 hr of incubation at 37°C and washed five times. Afterward, substrate solution 90 µL was added and then incubated for 15-25 min at 37°C and stop solution was added, turning the liquid yellow. Finally, the plate is checked and read at 450 nm by a microplate reader.

Statistical analysis: Data analysis was performed using GraphPad Prism® version 8. Data are shown as Mean±SD. One-way ANOVA was used for analysis, followed by a *post hoc* test to determine significant differences between groups. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean response times of the control group following a noxious thermal stimulus at 30, 60 and 90 min were (12.8±1.05, 13.1±1.09 and 12.1±1.39 sec), respectively. The corresponding values of GBP, BAC and SUM treated groups were (15.6±1.8, 14.8±1.90 and 14.9±2.1), (14.43±1.33, 15.55±1.4 and 13.45±1.07) and (13.2±1.4, 13.6±1.3 and 13.1±0.8), respectively. These values showed no significant differences in comparison to each other or to the control group (Table 1).

In the GBP-treated group, the mean time spent in paw licking (TS) after 30 min of drug administration during the acute and chronic phases (43.00±4.42 and 97.5±9.8, respectively) was significantly reduced when compared to the control group (68.83±2.1 and 251.5±6.0, respectively). Similarly, in the BAC-treated group, the mean TS values after 30 min of drug administration for the acute and chronic phases (59.17±1.4 and 138.6±8.1, respectively). Show significantly lower than the control group and significantly higher than the GBP-treated group. On the other hand, in the SUM-treated group, the mean TS value after 30 min of drug administration during the chronic phase (237±8.6) was reduced significantly compared to the control group, although the mean TS value during the acute phase showed no significant difference. Furthermore, the mean TS values in the SUM group were significantly increased in both phases relative to those in the GBP and BAC-treated groups (Table 2).

In the GBP-treated group, the mean reaction times after 30, 60 and 90 min of injection were 12.52±0.25, 12.52±0.27 and 10.55±0.32 sec, respectively. These values were increased significantly when compared to control postoperative group values (7.85±1.09, 7.31±0.97 and 7.45±1.12). Furthermore, compared to the normal control group, the mean reaction time at 90 min was significantly lower (12.66±0.77). However, at 30 and 60 min, the results for the control normal group (12.85±1.04, 13.06±1.05) and in the GBP-treated group were not significantly different within the group. Notably, the mean reaction time at 30 min was not significantly different from that at 60 min but was significantly increased when compared to the value at 90 min. On the other hand, in the BAC-treated group, the mean reaction times at 30, 60 and 90 min (9.98±0.26, 10.03±0.44 and 10.02±0.21 sec, respectively) significantly increased when compared with postoperative group values. Additionally, the values of reaction time in the BAC-group show a significant reduction when compared to the control normal group. Regarding the BAC-treated group, no significant differences were observed within the same group at any time point. Meanwhile, in the SUM-treated group, the mean reaction times at 30, 60 and 90 min (9.68±0.34, 10.00±0.31 and 8.85±0.39 sec, respectively) show significant increases compared to the values of the postoperative group and were also lower than the values of the control normal group. The SUM-treated group, reaction times showed no significant differences within the group at any time point. Statistics revealed that at 30 and 60 min, the values of mean reaction times of the GBP-treated group increased significantly compared to the BAC and SUM-treated group values. However, at 90 min, no significant differences were observed among the GBP, BAC and SUM groups (Table 3).

Table 1: Effect of intraperitoneal administration of sumatriptan (4 mg/kg), baclofen (4 mg/kg) and gabapentin (300 mg/kg) on noxious thermal stimulus in rats

	Group (N = 6)				
Time	Control	Gabapentin	Baclofen	Sumatriptan	p-value
At 30 min	12.8±1.05	15.6±1.8	14.43±1.33	13.2±1.4	NS
At 60 min	13.1±1.09	14.8±1.90	15.55±1.4	13.6±1.3	NS
At 90 min	12.1±1.39	14.9±2.1	13.45±1.07	13.1±0.8	NS

Reaction time is expressed in seconds as Mean±Standard Deviation (SD). N represents the number of animals per group (N = 6). Statistical analysis was performed using one-way ANOVA, followed by the Tukey-Kramer multiple comparisons test and NS: Non-significant differences (p>0.05)

Table 2: Effects of sumatriptan (4 mg/kg), baclofen (4 mg/kg) and gabapentin (300 mg/kg) on time spend in paw liking 30 min after dose administration during formalin test

	Group (N = 6)			
Time	Control	Gabapentin	Baclofen	Sumatriptan
Acute phase (0-10 min)	68.83±2.1	43.00±4.42^{A}	59.17±1.4^{A,B}	65.83±2.4^{B,C}
Chronic phase (0-10 min)	251.5±6.0	97.5±9.8^{A}	138.6±8.1^{A,B}	237.00±8.6^{A,B,C}

Reaction time is expressed in seconds as Mean±Standard Deviation (SD). Each value represents the mean reaction time. N represents the number of animals per group (N = 6). Statistical analysis was performed using one-way ANOVA, followed by the Tukey-Kramer multiple comparisons test. Symbols indicate statistical significance: ^{A}Significant difference from the control, ^{B}Significant difference from gabapentin and ^{C}Significant difference from baclofen. A p-value of <0.05 was considered statistically significant

Table 3: Effect of intraperitoneal injection of sumatriptan (4 mg/kg), baclofen (4 mg/kg) and gabapentin (300 mg/kg) in rats subjected to sciatic nerve ligation

	Group (N = 6)				
Time	Control	Control postoperative	Gabapentin	Baclofen	Sumatriptan
At 30 min	12.85±1.04	7.85±1.09[A]	12.52±0.25[B]	9.98±0.26[A,B,C]	9.68±0.34[A,B,C]
At 60 min	13.07±1.05	7.31±0.97[A]	12.52±0.27[B]	10.03±0.44[A,B,C]	10.00±0.31[A,B,C]
At 90 min	12.67±0.77	7.45±1.12[A]	10.55±0.32[A,B]	10.02±0.21[A,B]	8.85±0.39[A,B]

Reaction time is expressed in seconds as Mean±Standard Deviation (SD). Each value represents the mean reaction time. N represents the number of animals per group (N = 6). Statistical analysis was performed using one-way ANOVA, followed by the Tukey-Kramer multiple comparisons test. Symbols indicate statistical significance: [A]Significant difference from the control, [B]Significant difference from the control postoperative and [C]Significant difference from gabapentin. A p-value of <0.05 was considered statistically significant

Table 4: Effects of sumatriptan (4 mg/kg), baclofen (4 mg/kg) and gabapentin (300 mg/kg) on the level of GABA, GLU, SP and CGRP in rat brain tissue homogenates

	Group (N = 6)			
Group	Gaba (pg/mL)	Glutamate (nmol/g)	Substance p (pg mg)	CGRP (pg/mg)
Control	128.0±9.34	23.58±9.08	129.7±10.40	213.1±7.21
Gabapentin	149.6±6.30[A]	21.41±5.37	110.1±7.96[A]	184.5±10.98[A]
Baclofen	179.5±6.93[A,B]	18.56±0.60	120.8±9.47	210.0±13.29[B]
Sumatriptan	133.8±2.92[B,C]	21.74±3.03	112.3±8.21[A]	166.6±6.59[A,B,C]

Biomarker levels are expressed as Mean±Standard Deviation (SD). Each value represents the mean biomarker level. N represents the number of animals per group (N = 6). Statistical analysis was performed using one-way ANOVA, followed by the Tukey-Kramer multiple comparisons test. Symbols indicate statistical significance: [A]Significant difference from the control value, [B]Significant difference from gabapentin and [C]Significant difference from baclofen. A p-value of <0.05 was considered statistically significant

The mean GABA levels in the control, gabapentin, baclofen and sumatriptan groups were 128.0±9.347, 149.6±6.30, 179.5±6.93 and 133.8±2.92 pg/mL, respectively. Gabapentin and baclofen treatment show a significant increase in the GABA level ($p<0.05$) while sumatriptan treatment showed no significant difference compared to the control group. On the other hand, the mean glutamate levels in the control, gabapentin, baclofen and sumatriptan groups were 23.58±9.08, 21.41±5.37, 18.56±0.60 and 21.74±3.03 µmol/g, respectively, there are no significant differences observed within groups and controls. Meanwhile, the mean substance P levels in the control, gabapentin, baclofen and sumatriptan groups were 129.7±10.40, 110.1±7.96, 120.8±9.47 and 112.3±8.21 pg/mg, respectively. When compared to the control group, the gabapentin and sumatriptan groups exhibited a significant decrease in substance P, while baclofen treatment showed no significant difference. Furthermore, the mean CGRP levels in the control, gabapentin, baclofen and sumatriptan groups were 213.1±7.212, 184.5±10.98, 210.0±13.29 and 166.6±6.59 pg/mg, respectively. Both gabapentin and sumatriptan treatments significantly decreased CGRP levels, but baclofen treatment showed no significant difference compared to the control (Table 4).

DISCUSSION

This research assesses the effects of sumatriptan (SUM), baclofen (BAC) and gabapentin (GBP) on both acute thermal nociception and chronic neuropathic pain models in rats. The study used the plantar test analgesia meter and the formalin test to assess pain behaviors. Additionally, it explored the impact of these drugs on key neurotransmitters and neuropeptide pain processing such as GABA, glutamate, substance P and CGRP. The results showed that 300 mg/kg of gabapentin (GBP) did not show a significant effect on the rats' tolerance to acute thermal nociception. This finding aligns with previous studies in mice, which also revealed that gabapentin shows no significant effect on withdrawal latency in the hot-plate test, a common model for assessing acute thermal nociception[11]. Similarly, high doses of gabapentin (300 mg/kg intraperitoneally) in the Tail-Flick Test produced a statistically significant, though minimal, increase in tail withdrawal latency[12]. However, the current study shows that gabapentin doses of 100 and 300 mg/kg significantly reduced pain sensitivity in a sciatic nerve ligation rat model. The analgesic effect was sustained throughout the experiment (at 30, 60 and 90 min post-injection), with the maximum effect observed at 60 min after administration. This is consistent with previous research demonstrating significant analgesic effects of gabapentin in neuropathic pain models. For example, Bannister *et al.*[13] found that gabapentin reduced both mechanical and thermal evoked pain behaviors, with effects observed from 20 to 120 min post-administration. In a diabetic neuropathic pain model in rats, gabapentin significantly increased hot-plate latency at a dose of 180 mg/kg compared to controls[14]. More studies, including Mangaiarkkarasi *et al.*[15], demonstrated that gabapentin reduced mechanical and thermal hypersensitivity in neuropathy models induced by drugs like paclitaxel.

In the formalin test, gabapentin at 300 mg/kg shows significantly reduced paw licking (TS) time spent during both the acute and chronic phases of pain, showing a notable analgesic effect. These findings align with those reported by Shannon *et al.*[16], who observed that gabapentin reduced behaviors in both phases of the formalin test, with effective doses ranging between 30 to 300 mg/kg. Regarding BAC, in the acute pain assessments, baclofen had no significant effect. However, it significantly reversed hyperalgesia and allodynia induced by sciatic nerve ligation at a dose of 4 mg/kg, with the effect being consistent at 30, 60 and 90 min post-injection. These findings align with studies showing that baclofen can produce dose-dependent analgesic effects. For example, Lee *et al.*[17] found that baclofen administered at low doses (0.001-0.01 µg intracisternal or intrathecally) did not alleviate thermal hyperalgesia in strychnine-treated rats. However, higher doses of baclofen are effective in reversing pain-related behaviors in various pain models. Britto *et al.*[18] demonstrated that baclofen exhibited a dose-dependent analgesic effect in the hot plate test, where higher doses (10 mg/kg) resulted in significant antinociception.

Current results are consistent with previous studies that examined baclofen in models of neuropathic pain. For example, Kohli *et al.*[19] found that baclofen significantly reduced both thermal and mechanical hyperalgesia at 30, 60 and 120 min post-administration in a rat CCI model. However, the effect on mechanical hyperalgesia diminished at 120 min. Additionally, Salte *et al.*[20] demonstrated that baclofen, administered subcutaneously at a dose of 10 mg/kg, reversed cold allodynia in rats with CCI. Baclofen's efficacy was further supported by studies showing significant antinociceptive effects at doses ranging from 5-10 mg/kg in neuropathic pain models[21].

On the other hand, the antimigraine drug sumatriptan did not show a significant effect on acute thermal pain in the current study. This result in agreement with previous studies done by Ottani *et al.*[22] reported that sumatriptan had no significant effect on acute pain in standard nociceptive tests, including the hot plate and writhing tests. Similarly, Nikai *et al.*[23] demonstrated that sumatriptan did not affect thermal or mechanical nociceptive thresholds in rats when tested with systemic (subcutaneous doses of 300-600 µg/kg) or direct spinal (intrathecal doses) administration. However, the present study showed that sumatriptan had an analgesic effect in chronic neuropathic pain models. The drug significantly alleviated pain at 30, 60 and 90 min post-administration in sciatic nerve ligation rats, suggesting its efficacy in managing chronic pain. These findings align with studies by Afshari *et al.*[24], who reported that in rats with spinal cord injuries, sumatriptan reduced neuropathic pain, improving both thermal and mechanical pain sensitivity. Sumatriptan has also been shown to reduce thermal allodynia in rats with vincristine-induced neuropathy[25] and improve mechanical thresholds in trigeminal neuropathic pain model[6].

Regarding neurotransmitter and neuropeptide analysis, our study demonstrated that gabapentin notably increased GABA levels and reduced substance P and CGRP levels, without significantly affecting glutamate levels. This result is consistent with findings by Cai *et al.*[26], who mentioned the effect of gabapentin increased GABA levels by 55.7% in the visual cortex but had no significant effect on glutamate levels. Fehrenbacher *et al.*[27] also showed that gabapentin selectively reduces the release of substance P and CGRP in spinal tissues under inflammatory conditions. These effects support the theory that gabapentin's action on pain is primarily through modulation of GABAergic activity and suppression of neuropeptide release during pathological states.

Baclofen, a GABA receptor agonist, significantly increased GABA levels in our study. These findings align with earlier studies demonstrating that baclofen increases GABAergic activity in the brain. Rastogi *et al.*[28] found that baclofen administered at 20 mg/kg increased GABA levels by 13% in the corpus striatum. However, baclofen had no significant effect on glutamate, substance P or CGRP levels in our study. This is in line with studies such as Morton *et al.*[29], which demonstrated that baclofen did not significantly alter the release of substance P or CGRP from the spinal cord during nociceptive stimulation, suggesting that its analgesic effects may be mediated through mechanisms other than inhibition of these neuropeptides.

In the present study, sumatriptan was found to significantly reduce substance P and CGRP levels, but it had negligible effects on GABA and glutamate. Arvieu *et al.*[30] demonstrated that sumatriptan inhibited the release of substance P and CGRP from primary afferent fibers through a presynaptic mechanism involving 5-HT1B/1D receptors. Current results corroborate these findings, suggesting that sumatriptan's analgesic effects are mediated by modulating neuropeptide release rather than by affecting excitatory neurotransmitter systems like glutamate.

CONCLUSION

Gabapentin was the most potent in both the formalin test and chronic pain models, influencing brain biomarkers such as GABA, substance P and CGRP. Baclofen was effective in reversing chronic pain, though less potent than gabapentin and did not affect acute thermal pain or neuropeptide

release. Sumatriptan showed effectiveness only in the second phase of the formalin test and in chronic pain models, with significant effects on substance P and CGRP but no impact on GABA or glutamate. Future studies should explore the long-term effects of gabapentin, baclofen and sumatriptan in diverse pain models, as well as investigate potential synergistic combinations to enhance therapeutic efficacy.

SIGNIFICANCE STATEMENT

This study discovered the effects of sumatriptan, baclofen and gabapentin on acute and chronic neuropathic pain, which can be beneficial for improving pain management strategies. This study will help researchers uncover critical areas of neuropathic pain treatment that many researchers have not been able to explore. Thus, a new theory on effective pain management and neuropeptide modulation may be arrived at.

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