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Comparative Analysis of Sciatic Nerve Ligation and Oxaliplatin-Induced Neuropathic Pain Models: Thermal Nociception and Inflammatory Mechanisms

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ABSTRACT

Neuropathic pain, resulting from damage or dysfunction of the nervous system, presents significant clinical challenges due to its chronic nature and resistance to treatment. This study compared the thermal nociception and inflammatory mechanisms of two neuropathic pain models: Sciatic nerve ligation (SNL) and oxaliplatin-induced peripheral neuropathy. Male Wistar Albino rats were randomly assigned to control, SNL, and oxaliplatin-induced neuropathy. The SNL model was established through partial sciatic nerve ligation, while oxaliplatin (4 mg/kg) was administered intraperitoneally twice weekly for four weeks. Thermal nociception was evaluated using tail-flick and hot-plate tests, and inflammatory markers (TNF-α and IL-1β) were measured in dorsal root ganglia (DRG) tissue and serum using ELISA. Thermal analgesia tests revealed that neuropathic pain symptoms appeared from the second week in the oxaliplatin group and the fourth week in both models ($p<0.05$). TNF-α and IL-1β levels were significantly elevated in the SNL and oxaliplatin groups compared to controls, with the highest TNF-α levels observed in the oxaliplatin group ($p<0.05$). These findings indicate that both models effectively induce neuropathic pain, with notable increases in pro-inflammatory cytokines in DRG and serum. The study examines the inflammatory mechanisms underlying neuropathic pain, providing insights into its pathophysiology and potential therapeutic approaches.

Keywords: Neuropathic pain, Sciatic nerve ligation, Oxaliplatin-induced neuropathy, Thermal nociception, Pro-inflammatory cytokines.

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Introduction

Neuropathic pain is a clinical condition that results from damage or dysfunction in the nervous system. It significantly impacts patients' quality of life and is often challenging to treat (1). This type of pain can impact both the peripheral and central nervous systems, often becoming chronic and leading to physical, emotional, and social challenges (2,3). The fundamental mechanisms underlying neuropathic pain include peripheral and central sensitization, inflammation, and neurotransmitter imbalances. Therefore, the strategies used in the treatment of neuropathic pain are typically complex and multifaceted (4).

Several experimental models have been developed to enhance our understanding neuropathic pain's underlying mechanisms and to formulate effective treatment strategies. These models simulate various etiological processes and are crucial for investigating pain's neurophysiological, biochemical, and behavioral characteristics The most used models for studying neuropathic pain include spinal nerve ligation (SNL), oxaliplatin-induced neuropathy, and chronic constriction injury (CCI) (5–7). Each model simulates distinct mechanisms of neuropathic pain, aiding researchers in understanding the development of pain and its response to treatment.

Sciatic nerve injury is a commonly used method to model injuries in peripheral nerves and the pain syndromes they cause(8). This model is induced by various methods, including nerve compression, transection, or partial ligation, and it mimics the mechanical allodynia, thermal hyperalgesia, and motor dysfunction that result from peripheral nerve damage. Models that utilize sciatic nerve injury are often preferred for elucidating the molecular mechanisms underlying peripheral neuropathies(9–11). On the other hand, oxaliplatin is a platinum-based chemotherapeutic agent utilized in cancer treatment, and peripheral neuropathy is a frequently observed side effect (12). Oxaliplatin-induced neuropathic pain models have been developed to enhance our understanding of chemotherapy-induced neuropathy. These models reflect clinical symptoms such as cold sensitivity, mechanical allodynia, and sensorimotor dysfunction (6,13). This model facilitates the simultaneous examination of both central and peripheral components of neuropathic pain, allowing for a comprehensive assessment of the underlying pathophysiological processes in this domain.

The dorsal root ganglion (DRG) is a crucial structure involved in transmitting sensory information from peripheral nerves to the central nervous system(14,15). In

the development of neuropathic pain, both peripheral nerve injury and chemotherapy-induced neurotoxicity have been shown to induce significant molecular and cellular changes in the DRG. In the literature, alterations in gene expression, neuronal hyperexcitability, and inflammatory processes at the DRG level have been prominently observed in models of chemotherapeutic agents, such as oxaliplatin-induced peripheral neuropathies and sciatic nerve injuries. This underscores the DRG as a critical structural and functional center in the mediation of neuropathic pain(16,17).

The role of inflammation in the pathogenesis of neuropathic pain is garnering increasing attention. Nerve damage and chemotherapy agents increase pro-inflammatory cytokines in the peripheral and central nervous systems. In this process, tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) levels are significantly elevated (18,19). These cytokines play a critical role in activating the molecular pathways that initiate neuropathic pain. TNF-α can increase oxidative stress and cause neuronal damage in nerve cells by binding to TNF receptors on the cell surface. In contrast, IL-1β can intensify pain by promoting microglial activation and central sensitization processes(18). Therefore, the examination of inflammatory markers is crucial for enhancing our understanding of the molecular basis of neuropathic pain and for developing targeted treatment strategies.

This study aims to compare the similarities and differences between a peripheral neuropathy model based on sciatic nerve injury and an oxaliplatin-induced neuropathic pain model. By examining the inflammatory molecular mechanisms that mediate pain, as well as the sensory and behavioral changes in both models, this research seeks to provide a more comprehensive understanding of the pathophysiology of neuropathic pain.

Material Method

Animals

The necessary authorization for this research was obtained from the Local Animal Experiments Ethics Committee of Sivas Cumhuriyet University, under approval number 13.02.2024-16. The study utilized a sample of 18 male Wistar Albino rats, each four months old and weighing between 230 and 250 grams. The rats were housed in cages designed to minimize stress, according to international guidelines. The animals were maintained in a climate-controlled environment that provided a 12-hour light/dark cycle, with a temperature range of 22 ± 2°C and a relative humidity of 53 ± 5%. The room was equipped with sound insulation to minimize external disturbances. The research was conducted between 9:00 AM and 5:00 PM, during which light and sound levels were continuously monitored. In our research, we chose to euthanize the animals using the method of decapitation without anesthesia. The primary reason for this choice was to prevent potential interactions between the administered anesthesia and our biochemical findings.

Oxaliplatin-Induced Peripheral Neuropathy

Oxaliplatin was obtained from Fortius Pharmaceutical Health Products Ltd. Co. (İstanbul, Türkiye). The effects of oxaliplatin on thermal analgesia were investigated using tail-flick and hot-plate tests. Oxaliplatin (4 mg/kg) was administered intraperitoneally twice a week for 4 weeks, specifically on the 1st, 2nd, 8th, 9th, 15th, 16th, 22nd, and 23rd days. Thermal analgesia tests were conducted before the initial drug application (Day 0, pre-test) and on the 2nd, 9th, 16th, 23rd and 30th days thereafter (6).

Surgical Intervention

A neuropathic pain model was established through the partial ligation of the sciatic nerve. The surgical procedures were performed in the Experimental Animals Laboratory at Sivas Cumhuriyet University. Anaesthesia was administered via intramuscular injections of ketamine at a dosage of 90 mg/kg and xylazine at a dosage of 3 mg/kg. A surgical incision approximately 1 cm in length was made on the biceps femoris under aseptic conditions. Subsequently, the sciatic nerve was accessed at the mid-thigh level of the right leg. The sciatic nerve was meticulously dissected from the surrounding connective tissues and securely ligated using a 4-0 chromic catgut. The incision was then closed with 4-0 silk sutures (7,20).

Analgesia Tests

Thermal nociception was assessed using the tail-flick and hot plate methods (May TF 0703 Tail-flick Unit, AHPi 0603 Analgesic HP, Commat). The tail-flick test was conducted by positioning the stimulus 3 cm from the tips of the rats' tails to evaluate the functionality of the spinal reflex arc. The duration of the tail-flick response was then measured in seconds (21). A cutoff latency of 30 seconds was established to minimize the risk of tissue damage. The subjects were placed on a heated surface maintained at a temperature of 53 ± 0.6 °C for the hot-plate test. The latency to the first behavioral response, either licking or jumping, was recorded as an indicator of the pain threshold. A cutoff time of 50 seconds was established to prevent potential injury to the paw. Measurements in rats treated with oxaliplatin were taken at 30 and 60 minutes, while measurements in rats with sciatic nerve ligation were conducted at 60 minutes (22,23).

Experimental Protocol

Rats were randomly divided into three groups. To establish a neuropathic pain model, oxaliplatin (administered i.p. at a dose of 4 mg/kg) and the sciatic nerve ligation method were applied to the rats. The progression of neuropathic pain in the rats was subsequently monitored over four weeks using thermal analgesia tests.

Determination of TNF-α and IL-1β Levels in DRG and Serum

Following the completion of the experimental measurements, the rats were sacrificed via cervical dislocation, and the DRG was extracted from the L4-S5 region of the spinal column. The DRG tissues were placed in petri dishes and subjected to three washes with cold phosphate-buffered saline (PBS) at a pH of 7.4. The samples were then homogenized in cold PBS using a mechanical homogenizer (SpeedMill PLUS; Analytik Jena) to ensure thorough mixing. Subsequently, the homogenized samples were centrifuged at 4000 rpm for 10 minutes at a temperature of 4°C. The resulting supernatants were employed for biochemical analyses, with total protein concentrations determined using the Bradford protein assay kit (SERVA, Heidelberg, Germany) (24). Blood samples were collected into serum tubes and centrifuged at 2000 rpm for 10 minutes. The resulting yellowish serum was then carefully separated.

Data Analysis

The outcomes were assessed using one-way analysis of variance (ANOVA) and repeated measures ANOVA, followed by a Tukey post hoc test (SPSS version 23.0 for Windows) to enable multiple group comparisons. All findings are presented as mean ± standard error of the mean (SEM). The threshold for statistical significance was set at $p < 0.05$.

Results

Effects of Sciatic Nerve Ligation and Oxaliplatin-Induced Neuropathic Pain Model on Thermal Analgesia

The nociceptive pain threshold in each rat was assessed using thermal analgesia tests, including the Tail Flick and Hot Plate methods.

It has been determined that signs of neuropathy in animals appeared after the administration of oxaliplatin, beginning in the second week and starting from the 60th minute ($p<0.05$; Figure 1). From the third week of oxaliplatin administration, neuropathic symptoms were observed in the Tail Flick test conducted at both the 30-minute and 60-minute marks ($p<0.05$; Figure 1). Neuropathic pain symptoms were observed in both the sciatic nerve ligation and oxaliplatin-induced groups beginning in the fourth week ($p<0.01$; Figure 1). In the control group, the values on day 9 increased significantly compared to those on day 2 ($p = 0.013$). However, no significant differences were observed between day 16 and day 2 ($p = 0.226$) or between day 16 and day 9 ($p = 0.145$). Therefore, the significant changes observed on days 9 and 16 are believed to be attributable to the decrease in the neuropathic groups rather than to transient fluctuations in the control group. In the hot-plate test, it was observed that neuropathic symptoms developed in all groups within the neuropathic pain model, beginning in the second week ($p<0.05$; Figure 2).

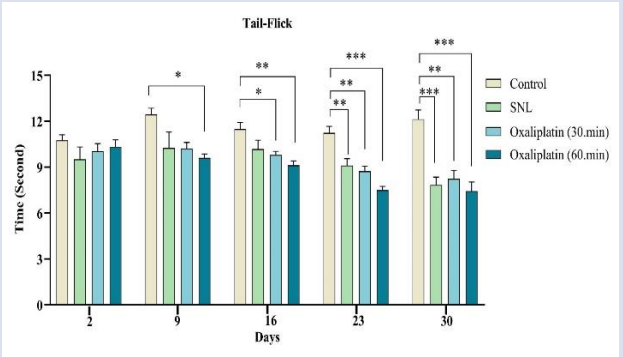

Figure 1. The data demonstrate the impact of SNL and oxaliplatin-induced neuropathic pain on nociception, as evaluated through tail flick tests. The values are presented as means ± SEM (n = 6). *p < 0.05, **p < 0.01, ***p < 0.001, reflecting a significant difference compared to the control group.

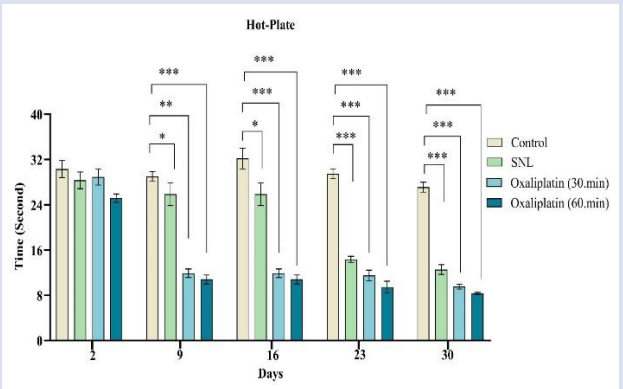

Figure 2. The data demonstrate the impact of SNL and oxaliplatin-induced neuropathic pain on nociception, as evaluated through hot plate tests. The values are presented as means ± SEM (n = 6). *p < 0.05, **p < 0.01, ***p < 0.001, reflecting a significant difference compared to the control group.

The Effect of Sciatic Nerve Ligation and Oxaliplatin-Induced Neuropathic Pain Models on Inflammatory Markers

The TNF-α level, measured in DRG tissue as an inflammatory marker, shows a significant difference between groups according to the statistical analysis results ($p<0.05$; Figure 3A). It has been determined that the group with the highest level of TNF-α is the one that received oxaliplatin treatment ($p<0.001$; Figure 3A). Comparing TNF-α levels between the SNL and oxaliplatin groups, it was observed that TNF-α levels were elevated in the oxaliplatin group ($p<0.05$; Figure 3A). When examining serum TNF-α levels, a significant increase was observed in both the SNL group and the Oxaliplatin group compared to the control group ($p<0.01$; Figure 3B).

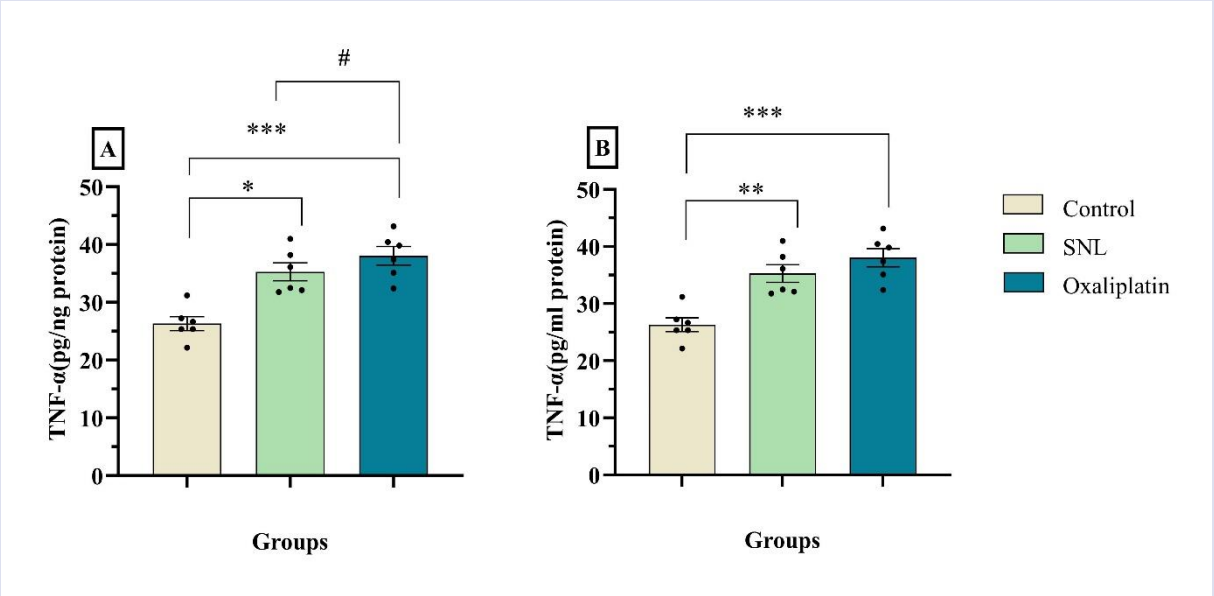

Figure 3. The data demonstrate the effects of SNL and oxaliplatin-induced neuropathic pain on (A) DRG and (B) serum levels of TNF-α, as assessed by ELISA. The values are presented as means ± SEM (n = 6). *p < 0.05, **p < 0.01, ***p < 0.001, reflecting a significant difference compared to the control group.

IL-1β measured using the ELISA method in DRG tissue demonstrated a significant difference between the groups (p<0.05; Figure 4A). The analysis revealed that the concentrations of IL-1β were significantly elevated in both the SNL and oxaliplatin groups compared to the control group (p<0.05; Figure 4A). Serum IL-1β levels were assessed across the groups, showing significantly elevated levels in both the SNL and Oxaliplatin groups (p<0.05; Figure 4B).

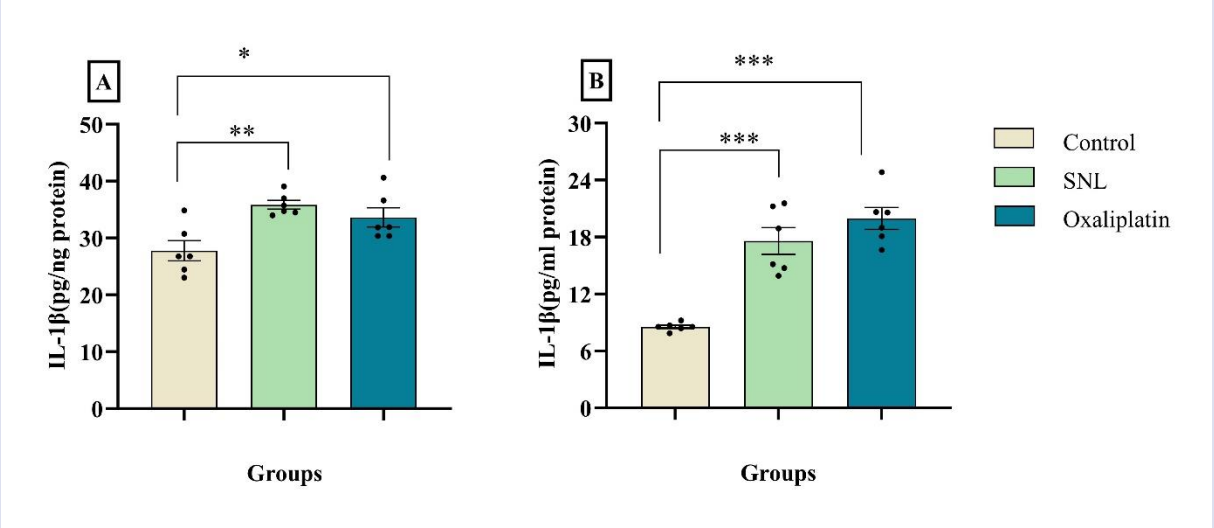

Figure 4. The data demonstrate the effects of SNL and oxaliplatin-induced neuropathic pain on (A) DRG and (B) serum levels of IL-1β, as assessed by ELISA. The values are presented as means ± SEM (n = 6). *p < 0.05, **p < 0.01, ***p < 0.001, reflecting a significant difference compared to the control group.

Discussion

This study demonstrates that thermal analgesia tests (Tail Flick and Hot Plate methods) conducted in models of sciatic nerve ligation and oxaliplatin-induced neuropathic pain indicate that symptoms of neuropathic pain began to develop in both models starting from the second week. The oxaliplatin group (second week) showed neuropathic symptoms earlier than the SNL group (fourth week). Inflammatory markers, specifically TNF-α and IL-1β, were significantly elevated in both models within the DRG and serum when compared to the control group. Furthermore, the oxaliplatin group demonstrated higher levels of TNF-α than the SNL group.

Our data suggest that the earlier onset of neuropathic symptoms in the oxaliplatin group aligns with the established toxic effects of oxaliplatin on peripheral nerves. This indicates that nociceptive pathways are

affected and altered more rapidly. Several studies in the literature have emphasized the ability of oxaliplatin to disrupt axonal integrity and induce peripheral nerve dysfunction (25,26). Research findings reveal that oxaliplatin causes damage to peripheral nerves, and this effect is mediated through mechanisms including inflammation, oxidative stress, mitochondrial dysfunction, and disruptions in axonal transport (27–29). These mechanisms can lead to rapid energy depletion and dysfunction in nerve cells. Sciatic nerve ligation typically results in more localized damage, while oxaliplatin exerts a systemic effect. This distinction can influence both the onset duration and the distribution of pain (30). This may consequently accelerate the onset of neuropathic symptoms in oxaliplatin-induced neuropathy by influencing both the timing of onset and the distribution of pain. Furthermore, oxaliplatin leads to cellular hyperactivity, particularly by affecting voltage-dependent Na^+ and Ca^{2+} channels (31,32). This alteration can result in abnormal electrical signalling in nerve cells and increased pain sensitivity. Consequently, these effects may lead to a more rapid onset of neuropathic pain compared to the ligation model.

Studies have demonstrated that inflammation plays a crucial role in the development of neuropathic pain, as indicated by elevated levels and activation of pro-inflammatory cytokines such as TNF-α and IL-1β. These cytokines contribute to the sensitization of pain pathways by promoting neuroinflammatory processes in both the peripheral and central nervous systems, thereby exacerbating pain perception and neuronal dysfunction (19). The data obtained from the study indicate that elevated levels of TNF-α and IL-1β are associated with a strong pro-inflammatory response in both models. These cytokines are known mediators of neuropathic pain and contribute to sensitization and hyperalgesia by activating immune and glial cells in the DRG (19,33). The considerable increase in inflammatory cytokines, particularly TNF-α and IL-1β, observed in both models underscores the potential benefits of anti-inflammatory therapies that target these pathways. The observed differences in TNF-α levels between SNL and oxaliplatin models suggest potential variations in the mechanisms underlying neuropathy in traumatic and chemotherapy-induced pain models. These findings suggest that, although similar inflammatory responses are observed in both models, different pathways may be involved. This distinction could play an important role in the development of treatments for neuropathic pain.

In conclusion, the elevation of inflammatory cytokines, such as TNF-α and IL-1β, in both models suggests the potential advantages of anti-inflammatory therapies. Additionally, the rapid onset of neuropathic symptoms associated with oxaliplatin treatment emphasises the necessity for early intervention. While this study concentrated on TNF-α and IL-1β to characterize the inflammation profile, analyses of other cytokines and chemokines could yield further insights. Moreover, long-term studies are needed to explore the progression and chronic effects of neuropathy.

Conflicts of interest

There are no conflicts of interest in this work.

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Ethical Approval Statement

The necessary authorization for this research was obtained from the Local Animal Experiments Ethics Committee of Sivas Cumhuriyet University, under approval number 13.02.2024-16.

References

[1] Koetsier E., Franken G., Debets J., Heijmans L., van Kuijk S. M. J., Linderoth B., Joosten E. A., Maino P., Mechanism of dorsal root ganglion stimulation for pain relief in painful diabetic polyneuropathy is not dependent on GABA release in the dorsal horn of the spinal cord, *CNS Neuroscience & Therapeutics,* 26(1) (2020) 136–143.

[2] Ozturk A., Sabanciogullari V., Tastemur Y., Oztoprak I., Evaluation of thalamus volumes in patients with diabetic polyneuropathy using magnetic resonance imaging method. *Cumhuriyet Science Journal,* 43(4) (2022) 569–576.

[3] Devor M., Neuropathic pain and injured nerve: Peripheral mechanisms, *British Medical Bulletin,* 47(3) (1991) 619–630.

[4] Kocot-Kępska M., Zajączkowska R., Mika J., Wordliczek J., Dobrogowski J., Przeklasa-Muszyńska A., Peripheral mechanisms of neuropathic pain—The role of neuronal and non-neuronal interactions and their implications for topical treatment of neuropathic pain, *Pharmaceuticals,* 14(2) (2021) 77.

[5] Fonseca-Rodrigues D., Laranjeira I., Barbosa J., Lamas N. J., Amorim D., Almeida A., Nociceptive, emotional, electrophysiological, and histological characterization of the chronic constriction injury model in female Wistar Han rats, *Brain Research Bulletin,* 167 (2021) 56–70.

[6] Sakurai M., Egashira N., Kawashiri T., Yano T., Ikesue H., Oishi R., Oxaliplatin-induced neuropathy in the rat: Involvement of oxalate in cold hyperalgesia but not mechanical allodynia, *Pain,* 147(1) (2009) 165–174.

[7] Joha Z., Yıldırım Ş., Hacısüleyman L., Taşkıran A.Ş., Investigation of the analgesic properties L-759,633 and SER 601 in experimental neuropathic pain model in rats and their comparison with pregabalin, *Cumhuriyet Science Journal,* 44(1) (2023) 41–45.

[8] Hacısüleyman L., Saraç B., Joha Z., Analgesic effects of vilazodone, indatraline, and talsupram in a rat model of neuropathic pain, *Turkish Journal of Pharmaceutical Sciences,* 19(3) (2022) 336–342.

[9] Wang B. B., Guo C., Sun S. Q., Zhang X. N., Li Z., Li W. J., Li Z., Schumacher M., Liu S., Comparison of the nerve

regeneration capacity and characteristics between sciatic nerve crush and transection injury models in rats, *Biomedical and Environmental Sciences,* 36(2) (2023) 160–173.

[10] Suter M. R., Papaloïzos M., Berde C. B., Woolf C. J., Gilliard N., Spahn D. R., Decosterd I., Development of neuropathic pain in the rat spared nerve injury model is not prevented by a peripheral nerve block, *Anesthesiology,* 99(6) (2003) 1402–1408.

[11] Medeiros P., Dos Santos I. R., Júnior I. M., Palazzo E., da Silva J. A., Machado H. R., Ferreira S. H., Maione S., Coimbra N. C., de Freitas R. L., An adapted chronic constriction injury of the sciatic nerve produces sensory, affective, and cognitive impairments: A peripheral mononeuropathy model for the study of comorbid neuropsychiatric disorders associated with neuropathic pain in rats. *Pain Medicine,* 22(2) (2021) 338–351.

[12] Cersosimo R. J., Oxaliplatin-associated neuropathy: A review, *Annals of Pharmacotherapy,* 39(1) 128–135.

[13] Egashira N., Pathological mechanisms and preventive strategies of oxaliplatin-induced peripheral neuropathy, *Frontiers in Pain Research,* 2.

[14] Ozsoy S., Ozdemir E., Gunes H., Gevrek F., Gulmez K., Ondansetron and AS19 attenuate morphine tolerance by modulating serotonin 5-HT3 and 5-HT7 receptor expressions in rat dorsal root ganglia, *J. Radiat Res. Appl. Sci.,* 16(4) (2023) 100682.

[15] Ciltas A.C., Ozdemir E., Gunes H., Ozturk A., Inhibition of the TRPM2 cation channel attenuates morphine tolerance by modulating endoplasmic reticulum stress and apoptosis in rats, *Neurosci Lett.*, 851 (2025) 138168.

[16] Zhao L., Jiang C., Yu B., Zhu J., Sun Y., Yi S., Single-cell profiling of cellular changes in the somatic peripheral nerves following nerve injury, Front Pharmacol., (2024) 15.

[17] Sun W., Hao Y., Li R., Ho I.H.T., Wu S., Li N., Comparative Transcriptome of Dorsal Root Ganglia Reveals Distinct Etiologies of Paclitaxel- and Oxaliplatin-induced Peripheral Neuropathy in Rats. Neuroscience, 516 (2023) 1–14.

[18] Nadeau S., Filali M., Zhang J., Kerr B. J., Rivest S., Soulet D., Iwakura Y., de Rivero Vaccari J. P., Keane R. W., Lacroix S., Functional recovery after peripheral nerve injury is dependent on the pro-inflammatory cytokines IL-1β and TNF: Implications for neuropathic pain, *The Journal of Neuroscience,* 31(35) (2011) 12533–12542.

[19] Leung L., Cahill C. M., TNF-α and neuropathic pain: A review. *Journal of Neuroinflammation,* 7(1) (2010) 27.

[20] Malmberg A. B., Basbaum A. I., Partial sciatic nerve injury in the mouse as a model of neuropathic pain: Behavioral and neuroanatomical correlates, *Pain,* 76(1) (1998) 215–222.

[21] Baser T., Ozdemir E., Filiz A. K., Taskiran A. S., Ghrelin receptor agonist hexarelin attenuates antinociceptive tolerance to morphine in rats, *Canadian Journal of Physiology and Pharmacology,* 99(5) (2021) 461–47.

[22] Çetindağ Çiltaş A., Öztürk A. Effect of thiamine on morphine analgesia and tolerance in rats, *Cumhuriyet Medical Journal*, (2023).

[23] Dirik H., Taşkıran, A.Ş., Joha Z., Ferroptosis inhibitor ferrostatin-1 attenuates morphine tolerance development in male rats by inhibiting dorsal root ganglion neuronal ferroptosis, *Korean Journal of Pain,* 36(3) (2023) 233–246.

[24] Avci O., Ozdemir E., Taskiran A. S., Inan Z. D. S., Gursoy S., Metformin prevents morphine-induced apoptosis in rats with diabetic neuropathy: A possible mechanism for attenuating morphine tolerance, *Naunyn-Schmiedeberg's Archives of Pharmacology,* 395(11) (2022) 1449–1462.

[25] Park S. B., Cetinkaya Fisgin A., Argyriou A. A., Höke A., Cavaletti G., Alberti P., Axonal degeneration in chemotherapy-induced peripheral neurotoxicity: Clinical and experimental evidence, *Journal of Neurology, Neurosurgery & Psychiatry,* 94(11) (2023) 962–972.

[26] Argyriou A. A., Bruna J., Park S. B., Cavaletti G., Emerging pharmacological strategies for the management of chemotherapy-induced peripheral neurotoxicity (CIPN), based on novel CIPN mechanisms, *Expert Review of Neurotherapeutics,* 20(10) (2020) 1005–1016.

[27] Schellingerhout D., LeRoux L. G., Hobbs B. P., Bredow S., Impairment of retrograde neuronal transport in oxaliplatin-induced neuropathy demonstrated by molecular imaging, *PLoS One*, 7(9) (2012) e45776.

[28] Zheng H., Xiao W. H., Bennett G. J., Functional deficits in peripheral nerve mitochondria in rats with paclitaxel- and oxaliplatin-evoked painful peripheral neuropathy, Experimental Neurology, 232(2) (2012) 154–161.

[29] Fumagalli G., Monza L., Cavaletti G., Rigolio R., Meregalli C. Neuroinflammatory process involved in different preclinical models of chemotherapy-induced peripheral neuropathy, *Frontiers in Immunology*, 11 626687.

[30] Park S. B., Lin C. S. Y., Krishnan A. V., Goldstein D., Friedlander M. L., Kiernan M. C., Oxaliplatin-induced neurotoxicity: Changes in axonal excitability precede development of neuropathy, *Brain,* 132(10) (2009) 2712–2723.

[31] Grolleau F., Gamelin L., Boisdron-Celle M., Lapied B., Pelhate M., Gamelin E., A possible explanation for a neurotoxic effect of the anticancer agent oxaliplatin on neuronal voltage-gated sodium channels, *Journal of Neurophysiology*, 85(5) (2001) 2293–2297.

[32] Kawashiri T., Egashira N., Kurobe K., Tsutsumi K., Yamashita Y., Ushio S., L-type Ca^{2+} channel blockers prevent oxaliplatin-induced cold hyperalgesia and TRPM8 overexpression in rats, *Molecular Pain,* 8 (2012) Article 7.

[33] Karabulut S., Filiz A. K., Akkaya R., Thiamine alleviates cognitive impairment and epileptogenesis by relieving brain inflammation in PTZ-induced kindling rat model, *Neurological Research,* 44(10) (2022) 902–909.