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Effect of Fenofibrate as PPARα Agonist in Suppressing the Development of Oxaliplatin-Induced Peripheral Neuropathy via TRPA1 Modulation

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Abstract

Background*: CIPN (Chemotherapy-induced Peripheral Neuropathy) primarily affects the sensory system and is accompanied by pain, autonomic dysfunction, and motor impairments. Alterations of intracellular second messengers at the supraspinal level in CIPN needed to be explored more. In addition, there is a lack of evidence regarding implications for the supraspinal area through the propagation of pain via the ascending pathway.* ***Objective****: In this study, we evaluated the effect of fenofibrate as a PPARα agonist in suppressing the development of CIPN.* ***Methods****: Twenty-four mice were distributed to the normal control group, neuropathy group, and neuropathy with the treatment of fenofibrate 75 and 150 mg/kg groups, resulting in 6 animals per group. Oxaliplatin was injected on days 0, 2, 4, and 6. The hot plate test was performed before the oxaliplatin administration and then continued on the 7th, 14th, and 21st days. Thalamus tissues were collected to measure the TRPA1 mRNA expression using qPCR.* ***Results****: Fenofibrate 75 mg/kg co-treatment with oxaliplatin tended to prevent the enhancement of oxaliplatin-induced thermal hyperalgesia in hind-paw withdrawal and rubbing responses. Furthermore, fenofibrate 75 and 150 mg/kg co-treatment with oxaliplatin significantly reduced the relative TRPA1 mRNA expression but did not modulate the relative BDNF mRNA expression in the thalamus.* ***Conclusion****: PPARα agonist has a potential effect in suppressing the development of CIPN. However, given the various perspectives on the role of neurotrophins in CIPN, additional non-clinical investigations, are needed to provide more insight into other mechanisms of CIPN and the role of PPAR agonists.*

Keywords*: fenofibrate, oxaliplatin, peripheral neuropathy, PPARα agonist, TRPA1*

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INTRODUCTION

Peripheral neuropathy affects approximately 2.4 percent of the population, and the frequency increases by 8% in the elderly population (Edwards *et al*., 2022). Diabetes mellitus, nerve damage, alcohol use, genetic disorders, dietary inadequacies, and chemotherapeutic drugs are commonly identifiable causes (Castelli *et al*., 2020). The term neuropathy, commonly known as chemotherapy, is called Chemotherapy-induced Peripheral Neuropathy (CIPN). The sensory system is primarily affected by CIPN, which is accompanied by motor impairment, autonomic dysfunction, and pain. Up to 70% of patients undergoing chemotherapy develop CIPN after or during treatment completion. Additionally, 30% of these individuals experienced this problem six months after chemotherapy (Seretny *et al*., 2014). Allodynia and hyperalgesia are predominant symptoms in patients with neuropathic pain. Both affect 15–50% of individuals with neuropathic pain in different forms of peripheral neuropathy and central pain disorders. (Jensen & Finnerup, 2014).

The mechanism by which chemotherapy damages the structure of the nervous system and results in CIPN is multifactorial and involves immunological processes, neuroinflammation, microtubule disorders, oxidative stress, mitochondrial damage, changes in ion channel activity, damage to the myelin sheath, and DNA damage (Areti *et al.*, 2014). Several classes of chemotherapy drugs, such as oxaliplatin, cause damage to the sensory and motor nerves, with the most significant prevalence in the platinum group (Burgess *et al*., 2021). Oxaliplatin exposure causes glial cell activation and enhances IL-1, IL-6, and TNF-α pro-inflammatory cytokines in neuropathic pain studies (Areti *et al.*, 2018; Lee *et al*., 2022; Wang *et al*., 2017). Upregulation of these proinflammatory cytokines triggers a condition called neuroinflammation. In peripheral areas, such as the dorsal root ganglion (DRG), neuroinflammation increases the expression of markers related to nociception and inflammation, such as BDNF and TRPA1, both through regulation of transcription and translation (Kameda *et al*., 2019; Lin *et al*., 2011). Ascending pathways in the dorsal horn spinal cord project information from peripheral sensory neurons in the DRG to supraspinal regions, such as the somatosensory cortex, thalamus, anterior cingulate cortex, insular cortex, and brainstem (Baron *et al*., 2010; Kocot-Kępska *et al*., 2021). Oxaliplatin increases the phosphorylation and upregulation of PKC gamma isoforms in the thalamus and PAG (Han & Smith, 2013). Using fMRI to measure brain activity, oxaliplatin induced hyperactivity in the S2 and insula (Nagasaka et al., 2017), as well as hyperactivity in the motor cortices, cingulate, and somatosensory neurons, as measured by increased p-Erk-IR neurons (Thibault *et al*., 2012). This pathological change in the supraspinal area is associated with oxaliplatin-induced peripheral neuropathy. Therefore, it is necessary to further investigate the changes in intracellular secondary messengers at the supraspinal level in CIPN.

Pain therapy for Peroxisome Proliferator-Activated Receptors (PPARs) is being widely developed. PPARs are nuclear receptors activated by endogenous substances, such as fatty acids and their derivatives or drugs. In humans, PPARs consist of three isotypes: α, β/δ, and γ. The PPARα and PPARγ subtypes have been widely studied and are associated with neuropathic pain (Okine *et al.*, 2019). PPARα modulates the inflammatory response. Under conditions of hyperalgesia, PPARα expression in the DRG decreases, implicating the upregulation of proinflammatory cytokines (D'Agostino *et al*., 2009; Wang *et al.*, 2018). In previous studies, endogenous and synthetic PPARα agonists reduced allodynia and hyperalgesia in animal models of neuropathy (Caillaud *et al*., 2021; D'Agostino *et al*., 2009; Impellizzeri *et al*., 2016). Fenofibrate, a PPARα agonist, also reversed hyperalgesia and allodynia in mouse models (Caillaud *et al*., 2021; Oliveira *et al*., 2007)

Although exogenous agonists, such as fenofibrate, have been demonstrated to target PPAR in studies using animals for peripheral neuropathy, there is a lack of studies regarding the implications for the supraspinal area through the propagation of pain via the ascending pathway. Therefore, exploring the potential of fenofibrate as a PPARα agonist is needed to support scientific evidence regarding the role of PPARα agonists in neuropathic pain. Here, we evaluated the effect of fenofibrate in suppressing CIPN development of CIPN through a hotplate behavior test in mice. Additionally, we explored the molecular mechanisms by which fenofibrate affects TRPA1 and BDNF nociceptive biomarkers.

MATERIALS AND METHODS

Materials

Oxaliplatin (Merck, Darmstadt, Germany; CAS 61825-94-3) was solubilized in dextrose monohydrate 5% (PT. Widatra Bhakti, Pasuruan, Indonesia). Oxaliplatin was administered intraperitoneally at a dose

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of 3 mg/kg on days 0, 2, 4, and 6. Fenofibrate (pharmaceutical grade obtained from PT. Kalbe Farma Tbk., Jakarta, Indonesia) was solubilized in Tween 80 (PT. Brataco, Surabaya, Indonesia). Fenofibrate was administered at 75 and 150 mg/kg intraperitoneally for eight days since day 0. Normal saline 0,9% (PT. Widatra Bhakti) was administered subcutaneously to prevent nephrotoxicity in the platinum group (Rachman et al., 2022). Figure 1 illustrates the experimental timeline and dosing regimens.

Method

Animals

DDY mice weighing 25–30 g and aged 5-6 weeks were used in this study. Twenty-four mice were distributed to the normal control group, neuropathy group, and neuropathy with fenofibrate 75 and 150 mg/kg treatment groups, resulting in six animals per group. The animals were housed in three mice per cage, and acclimatization was performed for a week. All mice were maintained under a 12:12 h diffuse light/dark cycle at a regulated temperature (25°C ± 2°C) and humidity (60 ± 10%), with free access to food and water. All experimental protocols were approved by the ethics committee of the Faculty of Veterinary Medicine at Universitas Airlangga (ethical number 2). KEH.023.03.2023.

Hot plate test

The hot plate test was first performed one day before the induction of oxaliplatin as a baseline and then continued on days 7th, 14th, and 21st days. Before testing, the mice were habituated to the test room for 30 min. The test was carried out in a quiet room and hotplate setting at a constant temperature of 52 ± 1 ℃ to induce a response to heat. Heat inductors were applied to both plantar surfaces of the feet of the experimental mice and were placed on the metal surface of the hot plate. for 30 s as the cutoff time to avoid tissue damage (Kudla et al., 2019). The response to pain in experimental mice was based on visual observations of standing, licking, lifting the legs, jumping, and rubbing. The first latency time to a thermal stimulus was expressed as paw withdrawal latency (PWL). Three replicates of the test were performed at intervals of 15 min. (Hidayati et al., 2018).

Quantitative polymerase chain reaction (qPCR)

The animals were euthanized by decapitation 21 days after the first injection of oxaliplatin. Thalamus tissues were obtained, directly stored in liquid nitrogen, and stored at − 80 ◦C. The Total RNA Purification Kit (Jena Bioscience, Jena, Germany) was used to isolate RNA. RNA concentration was measured using a Quantus Fluorometer (Promega, Madison, WI, US). A GoScriptTM Reverse Transcriptase Kit (Promega) was used for reverse transcription to generate cDNA. Quantitative real-time PCR (qRT-PCR) was used to quantify the mRNA expression of TRPA1 (5′-GTACTTCTTGTCGTGTTTCTTGC-3′ for forward primer; 5′-ACCATCGTGTATCCAAATAGACC-3′ for reverse primer) and BDNF (5'-ATCCCATGGGTTACACGAAGGAAG-3' for forward primer; 5'-AGTAAGGGCCCGAACATACGATTG-3' for reverse primer). Using β-actin (forward primer:5'-TTCTTGGGTATGGAATCCTGT-3’; reverse primer:5’-AGCACTGTGTTGGCATAGAG-3’) as a reference gene, TRPA1 and BDNF mRNA expression levels were normalized. The GoTaq RT qPCR Master Mix Kit (Promega) was used for the qRT-PCR. Quantification of cycle threshold (Ct) values using the 2-ΔΔCt formula was used to evaluate changes in the mRNA expression of the gene of interest.

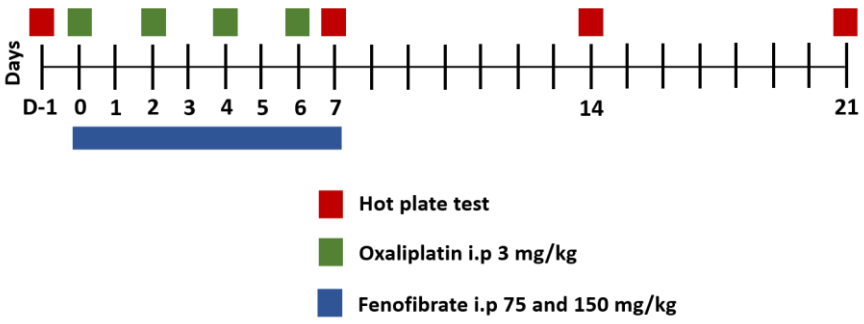

Figure 1. Timeline and dosing regiment of the experiment. Following baseline behavioral measurements on D-1, mice were given an intraperitoneal injection of oxaliplatin 3 mg/kg e on days 0, 2, 4, and 6 to induce peripheral neuropathy. On days D-1, 7, 14, and 21, behavioral assays using a hot plate test were performed. Fenofibrate of 75 and 150 mg/kg were injected for eight days since day 0 until day 7. Animals were sacrificed on day 21, and the DRGs were collected

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Statistical analysis

Data are displayed as the mean ± SEM using GraphPad Prism 9.0.2. Two-way ANOVA was used to calculate the statistics for the hot plate test, followed by Tukey's post hoc test. One-way ANOVA and Tukey post hoc tests were used to analyze the qPCR data. Differences were considered significant at p 0.05 (95% confidence).

The results of rubbing behavior showed that oxaliplatin significantly induced thermal heat hyperalgesia, as reflected by the reduced latency time on days 14 and 21, compared to the normal group (Figure 3). The neuropathy group tended to develop thermal heat hyperalgesia on days 7, 14, and 21 compared to baseline. Administration of 75 and 150 mg/kg fenofibrate reversed the reduction in rubbing response latency time induced by oxaliplatin. Meanwhile, the frequency parameter showed that exposure to oxaliplatin in the neuropathy group increased rubbing frequency on day 7 and significantly on days 14 and 21 compared to the control group. The rubbing frequency tended to increase in the neuropathy group on days 7, 14, and 21 compared to that in the neuropathy group at baseline. Meanwhile, the administration of fenofibrate at doses of 75 and 150 mg/kg tended to increase the rubbing frequency compared to the neuropathy group on days 7, 14, and 21.

The results of the jumping-off behavior test showed no significant differences in all treatment groups at each time point (Figure 4). Similar results were observed for both latency time and frequency. In this study, the administration of oxaliplatin and fenofibrate co-treatment did not affect jumping behavior when using a hot plate.

Oxaliplatin administration significantly decreased hind paw withdrawal latency time compared to that in the normal group and induced thermal heat hyperalgesia (Bhardwaj et al., 2016). Previous studies have shown that oxaliplatin reduces thermal hyperalgesia with a jumping-off response in cold hyperalgesia, but not in heat hyperalgesia (Renn *et al*., 2011). Another study showed the same result (Bouchenaki et al., 2021). Therefore, this behavioral test showed that oxaliplatin induction significantly induced thermal hyperalgesia in hind-paw withdrawal and rubbing responses, but not in jumping-off responses.

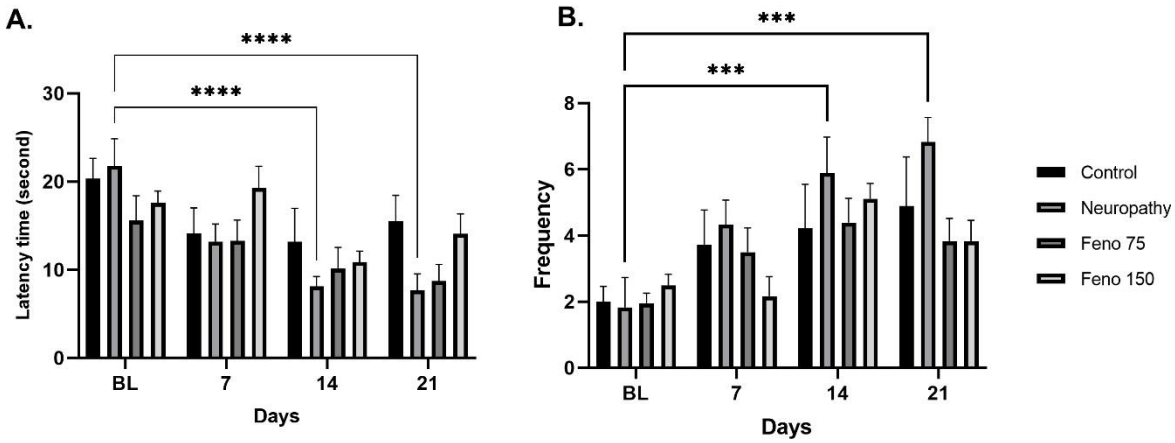

Figure 2. Fenofibrate's effect on thermal hyperalgesia caused by oxaliplatin on hind-paw withdrawal responses, with parameters for latency time (Figure 1A) and frequency (Figure 1B). Statistical significance between treatment groups is indicated by ***p<0.001 and ****p<0.0001 (two-way ANOVA followed by Tukey's post-hoc test; n = 6 mice)

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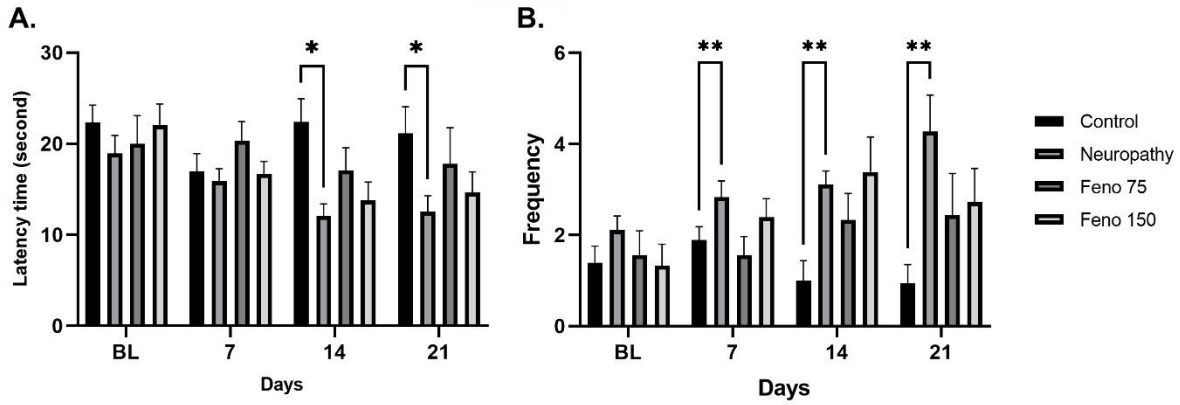

Figure 3. Fenofibrate's effect on thermal hyperalgesia caused by oxaliplatin on rubbing responses, with parameters for latency time (Figure 1A) and frequency (Figure 1B). Statistical significance between treatment groups is indicated by *p<0.05 and **p<0.01 (two-way ANOVA followed by Tukey's post-hoc test; n = 6 mice)

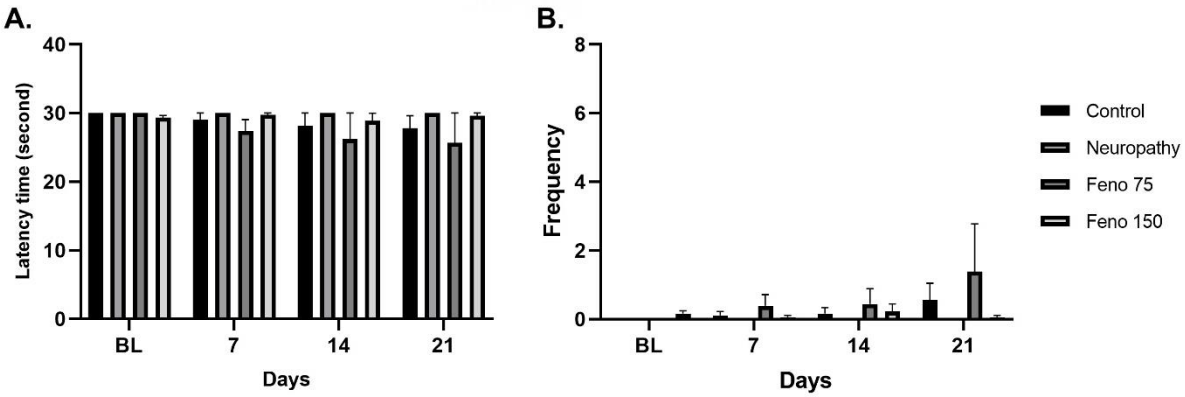

Figure 4. Fenofibrate's effect on thermal hyperalgesia caused by oxaliplatin on jumping-off responses, with parameters for latency time (Figure 1A) and frequency (Figure 1B). No significant differences in treatment groups were identified (two-way ANOVA followed by Tukey's post-hoc test; n = 6 mice)

Approximately 12 different types of behavior have been recorded in the hot-plate test, including sniffing, rearing, licking, stamping, jumping, hindleg-withdrawal, leaning posture, grooming, and freezing (Espejo & Mir, 1993). Although variances were observed depending on the type of measured activity, some of these behaviors were sensitive to particular analgesics or drugs. (Deuis et al., 2017). Forepaw withdrawal typically occurs first, and hindpaw withdrawal or licking is seen as a preferred sign of nociception. Forepaws are often biased and used in exploration because of their inconsistent contact with metal surfaces (Deuis et al., 2017; Minett *et al*., 2011). If no nocifensive behavior was observed within the 30 s cut-off time, the animal was removed from the hot plate to prevent tissue damage (Kudla et al., 2019).

Administration of 75 and 150 mg/kg fenofibrate in combination with oxaliplatin tended to prevent the enhancement of oxaliplatin-induced thermal hyperalgesia in hind-paw withdrawal and rubbing responses. This result correlates with other behavioral tests regarding the role of PPAR-alpha in neuropathy. PEA (Palmitoylethanolamide) and OEA (oleoylethanolamide) are endogenous PPARα agonists. PEA reduces mechanical and thermal hyperalgesia in mice with carrageenan-induced inflammation mice (Sasso et al., 2012). In HF-fed rats, PEA significantly decreased mechanical and thermal hypersensitivity (Wang *et al*., 2017). In a rodent model of chronic constriction injury, intraperitoneal administration of PEA for seven days reduced hyperalgesia (Bettoni et al., 2013). Moreover, mechanical and thermal thresholds in SNI mice were significantly enhanced by PEA and OEA treatments (Guida et al., 2015). The results of rubbing behavior showed that oxaliplatin significantly induced thermal heat hyperalgesia, as reflected by the reduced latency time on days 14 and 21, compared to the normal group (Figure 2). The neuropathy group tended to

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develop thermal heat hyperalgesia on days 7, 14, and 21 compared to baseline. Administration of fenofibrate (75 and 150 mg/kg) reversed the reduction in rubbing response latency time induced by oxaliplatin. Meanwhile, the frequency parameter showed that exposure to oxaliplatin in the neuropathy group increased rubbing frequency on day 7 and significantly on days 14 and 21 compared to the control group. The rubbing frequency tended to increase in the neuropathy group on days 7, 14, and 21 compared to that in the neuropathy group at baseline. Meanwhile, the administration of fenofibrate at doses of 75 and 150 mg/kg tended to increase the rubbing frequency compared to the neuropathy group on days 7, 14, and 21.

The effect of fenofibrate co-treatment against relative TRPA1 mRNA expression

To test the effects of oxaliplatin and fenofibrate co-treatment on TRPA1 mRNA expression in the thalamic tissue, we conducted a qPCR test. The results showed that oxaliplatin administration in the neuropathy group compared to the control increased TRPA1 mRNA expression in the thalamic tissue 21 days after the first oxaliplatin injection (Figure 5). This result is consistent with earlier studies that reported that oxaliplatin increased the expression of TRPA1 mRNA and protein in DRG tissue and played a crucial role in neuropathic pain in rodents (Chukyo et al., 2018; Park et al., 2015). Oxaliplatin sensitizes TRPA1 via cytosolic acidification of DRG sensory neurons (Riva et al., 2018). According to several studies, oxaliplatin increases the sensitivity of hTRPA1 by a mechanism involving the inhibiting prolyl hydroxylase and the oxidation of intracellular cysteines. (Miyake et al., 2016, 2017). In the periaqueductal region and thalamus, oxaliplatin causes mechanical allodynia by increasing the activation of PKC isoforms and causing phosphorylation of the γ/ε isoforms of PKC (Norcini et al., 2009). PKC activation increases TRPA1-mediated pain sensation (Bautista et al., 2006). These results confirm earlier research that TRPA1 expression is increased in the thalamus brain region by oxaliplatin-induced thermal hyperalgesia via a PKC-dependent mechanism, demonstrating the supraspinal role of oxaliplatin in neuropathic pain.

Administration of 75 and 150 mg/kg fenofibrate in combination with oxaliplatin significantly reduced the relative TRPA1 mRNA expression ($p<0.01$) compared to the neuropathy group. This result indicates that fenofibrate inhibited TRPA1 mRNA expression. IL-1, IL-6, and TNF were highly expressed in the DRG after treatment with oxaliplatin, and the administration of fenofibrate reduced the upregulation of these mRNAs (Caillaud *et al*., 2021; Campolo *et al*., 2021). IL-1β and TNFα induction increases TRPA1 expression in human IVD tissues (Kameda *et al*., 2019). In addition, TNFα elevated TRPA1 expression in cultured primary DRG neurons; however, at concentrations of 15 ng/ml and 50 ng/ml, it only gave less than 20% in TGNs (Meng et al., 2016). Based on the current study, the inhibition of TRPA1 mRNA expression by fenofibrate in the supraspinal area of the thalamus is possibly through the implication of the pathway in the peripheral region.

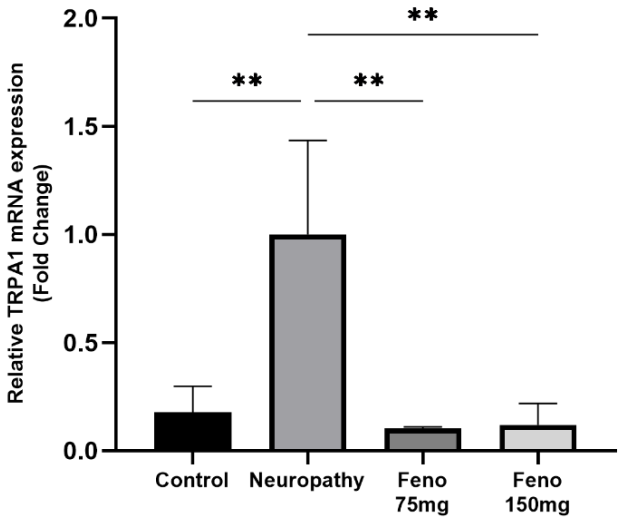

Figure 5. Quantitative RT-PCR testing of TRPA1 in the thalamus. **p < 0.01 indicates statistical significance between treatment groups (one-way ANOVA followed by Tukey's post-hoc test; n = 3 thalamus)

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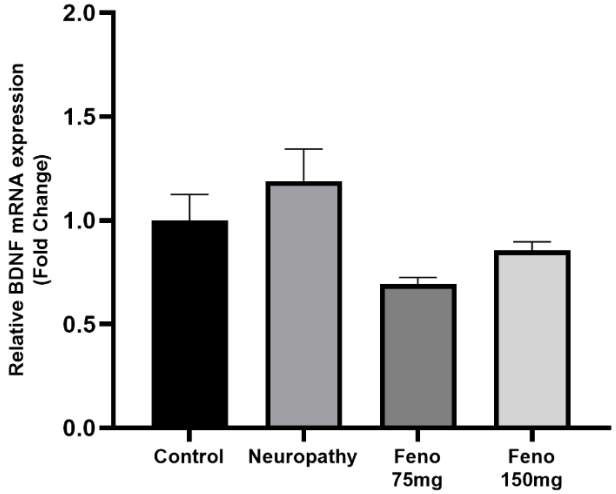

Figure 6. Quantitative RT-PCR testing of BDNF in the thalamus. No significant differences in treatment groups were identified. (one-way ANOVA; n = 3 thalamus)

The effect of fenofibrate co-treatment against relative BDNF mRNA expression

To test the effects of oxaliplatin and fenofibrate co-treatment on BDNF mRNA expression in the thalamic tissue, we conducted a qPCR test. The results demonstrated that, compared to the control group, the neuropathy group treated with oxaliplatin showed slightly enhanced BDNF mRNA expression 21 days after the initial oxaliplatin injection. (Figure 6). Administration of 75 and 150 mg/kg fenofibrate in combination with oxaliplatin decreased BDNF levels. Neurotrophic factors, such as BDNF, play a role in CIPN. However, this must be conclusively identified. Oxaliplatin significantly enhanced the expression of BDNF in the dorsal horn and DRG in previous research (Maruta et al., 2019; Ruyang et al., 2015). In a mouse model of chemotherapy-induced neuropathic pain, overexpression of BDNF in neurons contributes to the development of central sensitization (Ruyang et al., 2015). The expression of BDNF in the DRG is also increased by the elevation of pro-inflammatory cytokines under neuroinflammatory conditions (Lin *et al.*, 2011). In contrast, Campolo *et al.* (2021) found that oxaliplatin reduced BDNF and NGF in DRG samples, and treatment with PEA promoted BDNF and NGF release. These findings imply a role in facilitating the development and differentiation of new synapses and neurons. However, given the various prespectives regarding the role of neurotrophins in CIPN, additional non-clinical investigations are needed to provide more insight into other mechanisms of CIPN and the role of PPAR agonists.

TRPA1 upregulation correlates with CIPN progression. TRPA1 activation in cancer pain models increases hydrogen peroxide (H2O2) production, which maintains TRPA1 activation and sensitization; these H2O2 levels may be caused by increased NADPH oxidase and superoxide dismutase activity (Antoniazzi *et al*., 2019). Early TRPA1 inhibitor treatment prevents oxidative stress-induced CIPN, including PTX (Trevisan *et al*., 2013). As a result, the compound or drug targeting TRPA1 is promising for the prevention of CIPN. Although this research focused on the thalamus of the supraspinal area, more studies on other tissues and biomarkers provide a more integrative explanation of the CIPN mechanism.

CONCLUSION

The present findings indicate that oxaliplatin induction significantly induces thermal hyperalgesia in hind paw withdrawal and rubbing responses, but not in jumping-off responses. Administration of 75 and 150 mg/kg fenofibrate during oxaliplatin induction prevented the enhancement of oxaliplatin-induced thermal hyperalgesia. Moreover, fenofibrate significantly prevented oxaliplatin-induced upregulation of TRPA1. Therefore, PPARα agonist potential suppresses CIPN development. However, given the various prespectives regarding the role of neurotrophins in CIPN, additional non-clinical investigations need to be conducted to provide more insight into other mechanisms of CIPN and the role of PPAR agonists.

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AUTHOR CONTRIBUTIONS

Conceptualization, C. A., M. R., S.; Methodology, L. W., I. N. B. D., C. A.; Validation, A. N. A., P. A.; Formal Analysis, A. N. A., P. A., I. N. B. D.; Investigation, A. N. A., P. A., A. A. S. D. P., T. D. S., G. L. P., L. W.; Resources, C. A., M. R.; Data Curation, C. A., M. R, S.; Writing - Original Draft, A. A. S. D. P., T. D. S., G. L. P.; Writing - Review & Editing, A. N. A., P. A.; Visualization, A. N. A., P. A., A. A. S. D. P., T. D. S., G. L. P.; Supervision, C. A., M. R, S.; Project Administration, A. N. A., I. N. B. D., C. A., Funding acquisition, M. R., C. A.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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