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Research Article

Fenofibrate attenuates peripheral neuropathic pain by suppressing neuroinflammation in the anterior cingulate cortex

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Abstract

Background: Chemotherapy-induced neuropathy is a frequent complication of cancer treatment and significantly reduces patient quality of life. Neuroinflammatory processes in the anterior cingulate cortex (ACC) play a critical role in the modulation of pain sensitivity. Fenofibrate has demonstrated neuroprotective properties and has been proposed as a potential therapeutic agent for the management of peripheral neuropathy.

Materials and methods: A total of 20 male BALB/c mice were divided into four groups (five per group): control, neuropathy (oxaliplatin, 3 mg/kg), neuropathy + fenofibrate (150 mg/kg), and neuropathy + fenofibrate (300 mg/kg). A behavioral test using von Frey filaments was used to assess mechanical allodynia. mRNA expression of ionized calcium-binding adapter molecule 1 (IBA-1), tumor necrosis factor-alpha (TNF-α), and caspase-3 in the ACC was measured using RT-qPCR.

Results: Fenofibrate at doses of 150 and 300 mg/kg improved the mechanical withdrawal threshold, followed by significant alterations in the mRNA expression of IBA-1, TNF-α, and caspase-3.

Conclusion: Fenofibrate ameliorates chemotherapy-induced neuroinflammation and neuronal apoptosis in the ACC.

Keywords

anterior cingulate cortex, cancer, chemotherapy, fenofibrate, peripheral neuropathy

Introduction

Peripheral neuropathy is one of the neurological disorders and affects approximately 30% of patients, especially in the elderly population (Hanewinckel et al. 2016). Chemotherapy-induced peripheral neuropathy (CIPN) is one of the serious side effects of chemotherapy administration and is characterized by peripheral neuronal damage (Lehmann et al. 2020; Salat 2020). Approximately 73% of patients experience this adverse effect, particularly with platinum-based chemotherapeutic agents such as cisplatin, carboplatin, and oxaliplatin (Burgess et al. 2021; Niaz et al. 2024). This condition is characterized by pain, numbness, tingling, allodynia, hyperalgesia, and motor dysfunction (Burgess et al. 2021; Aliyah et al. 2024; Niaz et al. 2024; Ege et al. 2024).

Administration of chemotherapy causes dysfunction of the dorsal root ganglia (DRG), which are responsible for sensory input and the transmission of pain signals from the periphery to the central nervous system (CNS) (Burgess et al. 2021). Recent studies have demonstrated that central areas are also involved in the development and persistence of neuropathic pain, including the anterior cingulate cortex (ACC) (Masocha 2015; Nashawi et al. 2016; Juarez-Salinas et al. 2019; Morris et al. 2019; Lee et al. 2024). This area is responsible for the affective-emotional aspects of pain perception and becomes highly active when receiving painful stimuli (Chen et al. 2014). Oxidative stress and inflammation are the primary mechanisms underlying CIPN (Zajączkowska et al. 2019; Li et al. 2021; Ege et al. 2024). In spared nerve injury (SNI) conditions, microglial activation and increased cytokine expression, e.g., IL-6 and TNF-α, occur in the ACC (Li et al. 2022). This condition disrupts the balance between pro-apoptotic and anti-apoptotic proteins, triggering neuronal apoptosis (Huang et al. 2025). Tan et al. (2018) reported that peripheral nerve injury led to neuronal loss in the ACC, as indicated by significantly elevated caspase-3 levels in the ACC. However, in the context of CIPN, the mechanisms of neuroinflammation and neuronal apoptosis in the ACC remain largely unexplored.

Peroxisome proliferator-activated receptor (PPAR) is a nuclear receptor that regulates inflammatory responses by inhibiting transcription factors such as NF-κB, ATF1, ATF4, and STAT (Zhou et al. 2022). Recent studies have highlighted the therapeutic potential of PPAR agonists in neuropathic conditions. Agonists of PPARα and PPARγ have been shown to reduce allodynia and hyperalgesia in the CIPN mouse model (Zhang et al. 2022a; Aliyah et al. 2023). Fenofibrate, a PPARα agonist, has been shown to exert neuroprotective effects by suppressing neuroinflammation and preserving mitochondrial integrity in in vivo studies (Esmaeili et al. 2016). However, research investigating the involvement of PPAR activation in neuroinflammatory processes within the ACC remains limited.

Based on these findings, previous studies have confirmed that fenofibrate, a PPARα agonist, attenuates chemotherapy-induced neuropathic pain. Activation of the PPARα pathway has been proven to ameliorate neuroinflammatory conditions. Nevertheless, further studies are needed to examine the effects of fenofibrate, a PPARα agonist, on CIPN, particularly in supraspinal regions such as the ACC. Therefore, the present study conducted a molecular analysis of fenofibrate administration on oxaliplatin-induced neuroinflammation and apoptosis in the ACC.

Materials and methods

Animals

A total of 20 male BALB/c mice aged 5–6 weeks and weighing 25–30 g were used in this study. The mice were randomly assigned to four groups (five per group): control, CIPN (oxaliplatin, 3 mg/kg), CIPN + fenofibrate (150 mg/kg), and CIPN + fenofibrate (300 mg/kg). Animals were acclimatized for one week before experimentation. Mice were housed under standard laboratory conditions with a 12-hour light/dark cycle at 24 ± 1 °C and 60 ± 10% relative humidity. Food and water were provided ad libitum. The experimental procedures were conducted in compliance with the Guidelines for the Care and Use of Laboratory Animals and the Declaration of Helsinki, with approval from the Animal Ethics Committee of the Faculty of Veterinary Medicine, Universitas Airlangga (Approval No. 2.KEH.023.03.2023).

Drug treatment

This study used drug treatment with oxaliplatin (Cat. No. O9512, Sigma-Aldrich, Merck KGaA, St. Louis, MO, USA) and fenofibrate (Cat. No. N/A, PT. Kalbe Farma Tbk., Jakarta, Indonesia). Oxaliplatin was diluted with dextrose monohydrate 5% (Cat. No. N/A, PT. Widatra Bhakti, Pasuruan, Indonesia), and fenofibrate was diluted with Tween 80 (Cat. No. N/A, PT. Brataco, Surabaya, Indonesia). Oxaliplatin (3 mg/kg), fenofibrate (150 mg/kg), fenofibrate (300 mg/kg), and solvent (dextrose monohydrate 5% + Tween 80) for the control group were injected intraperitoneally (i.p.).

Experimental design

This study consisted of four experimental groups (Fig. 1). Behavioral assessment using the von Frey test was performed, followed by molecular analysis using reverse transcription quantitative polymerase chain reaction (RT-qPCR). The experimental design (Fig. 1) employed oxaliplatin at a dose of 3 mg/kg, administered on days 1, 3, 5, and 7 to induce chemotherapy-induced peripheral neuropathy (CIPN). Based on previous studies, fenofibrate at doses of 150 and 300 mg/kg has been shown to exert a neuroprotective effect and to improve hyperalgesia (Assaf et al. 2020; Caillaud et al. 2021). In this study, fenofibrate was administered as a therapeutic intervention for CIPN after neuropathy had been established, from day 8 to day 15. The drug was administered therapeutically following

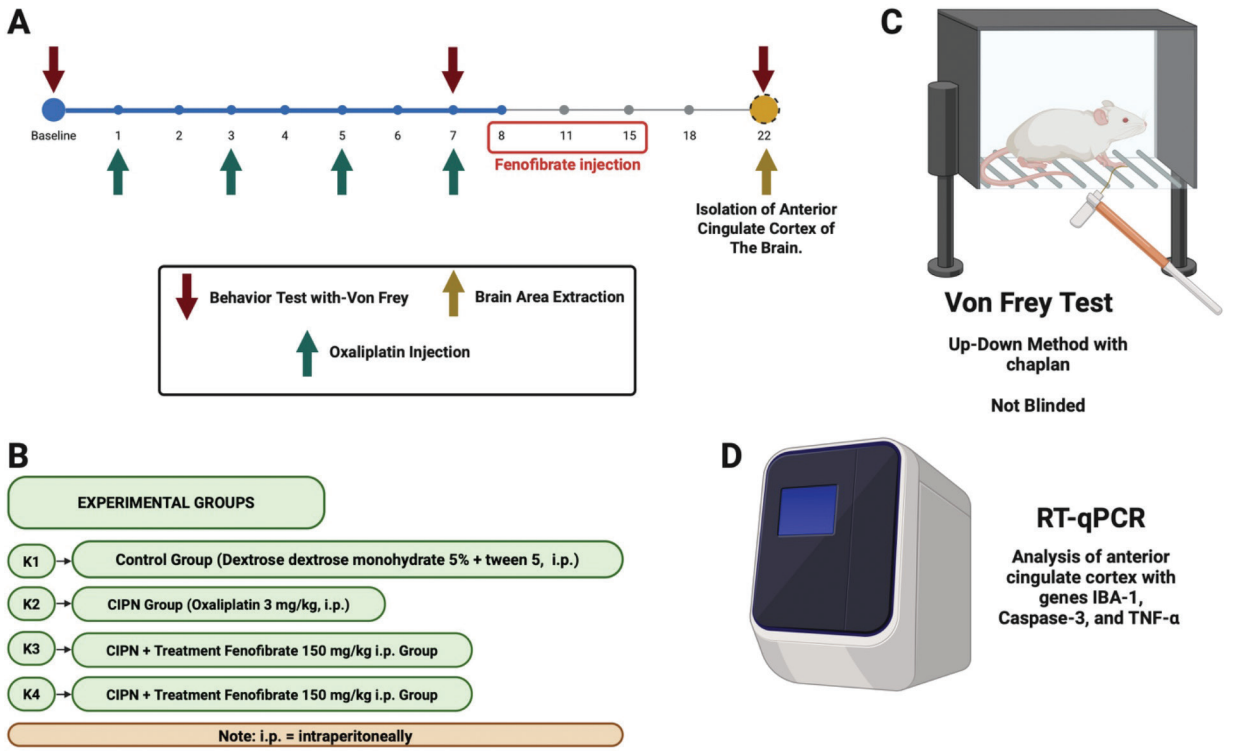

Figure 1. Experimental design. **A.** Experimental timeline; **B.** Experimental groups; **C.** von Frey test with up-down method using Chaplan; **D.** RT-qPCR.

the establishment of neuropathy. Behavioral testing using the von Frey assay was conducted at baseline, day 7, and day 22 to evaluate mechanical allodynia. Mechanical allodynia was assessed using the von Frey test, following the up-and-down method of Chaplan. The apparatus consisted of an acrylic box with a wire mesh floor, and calibrated von Frey filaments (0.02–2 g) were used for punctate stimulation. Filaments were applied perpendicularly to the plantar surface of the hind paw until the filament bent slightly and were held in place for approximately 2–3 seconds. A positive response was defined as paw withdrawal, rubbing, or licking. Each paw was tested for five trials according to the Chaplan algorithm, with an inter-stimulus interval of approximately 5 seconds. All behavioral assessments were conducted by an experimenter who was not blinded to the treatment groups. Von Frey testing was performed on days 0 (baseline), 7, and 22. Before the experiment began, mice were acclimated in the acrylic box for 15 minutes. Filament application began at 0.6 g, and the final mechanical withdrawal threshold was defined as the 50% withdrawal threshold.

Mice were euthanized on day 22 by decapitation, following approved ethical protocols. Brains were rapidly removed and placed on an ice-cold surface for dissection. The anterior cingulate cortex (ACC) was dissected according to stereotaxic coordinates defined in The Mouse Brain in Stereotaxic Coordinates by George Paxinos and Keith B. J. Franklin. Coronal sections corresponding to bregma +1.98 mm to +0.14 mm were identified using anatomical landmarks and sliced at 2 mm. The ACC was located in the medial prefrontal cortex, dorsal to the corpus callosum and medial to the motor cortex. The collected ACC samples were immediately snap-frozen in liquid nitrogen and stored at −80 °C until further molecular analysis.

This study also conducted molecular analysis using RT-qPCR on ACC samples. ACC samples were collected from mice sacrificed on day 22. Tissues were stored at −80 °C until analysis. RNA was extracted using an RNA purification kit (Cat. No. PP-210, Jena Bioscience, Jena, Germany), and cDNA synthesis was performed using a reverse transcription enzyme (Promega, Cat. No. A5001, Madison, WI, USA). SensiFAST® SYBR® No-ROX qPCR Master Mix (Cat. No. BIO-98005, Bioline, London, United Kingdom) was used to quantify gene expression on the MyGo Mini system. PCR amplification was performed using a thermal profile starting with polymerase activation at 95 °C for 2 minutes, followed by 40 cycles of denaturation at 95 °C for 15 seconds and annealing/extension at 60 °C for 1 minute. All primers were specifically designed using Primer-BLAST, and their sequences are listed in Table 1. Relative gene expression levels of IBA-1, caspase-3, and TNF-α were calculated using the 2^-ΔΔCT formula.

Table 1. The sequence of primers.

Genes	Primer sequences	PCR product
IBA-1 (F)	5'-GAATGATGCTGGGCAAGAGA-3'	84 bp
IBA-1 (R)	5'-CAGTTGGCTTCTGGTGTTC-3'	
Caspase-3 (F)	5-AGCAGCTTTGTGTGTGTGATTCTAA-3	137
Caspase-3 (R)	5-AGTTTCGGCTTTCCAGTCAGAC-3	
TNF-α (F)	5'-CTCCAGGCGGTGCCTATG-3'	149
TNF-α (R)	5'-GGGCCATAGAACTGATGAGAGG-3'	

Statistical analysis

Data are expressed as mean ± SEM and were analyzed using GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA), with statistical significance set at $p < 0.05$ (95% confidence level). Behavioral data from the von Frey test and caspase-3, IBA-1, and TNF-α mRNA expression were analyzed using one-way ANOVA followed by Dunnett's post hoc tests. This study also examined data distribution with normality and homogeneity tests before using two-way ANOVA for the behavioral test and one-way ANOVA for the molecular analysis.

Results

Effect of fenofibrate on neuropathic pain

Fig. 2A presents the pain response for all four groups. Two-way ANOVA revealed significant effects of treatment ($F(3.48) = 61.60$, $p < 0.0001$) and time ($F(2.48) = 167.8$, $p < 0.0001$), as well as a significant treatment × time interaction ($F(6.48) = 22.34$, $p < 0.0001$). Baseline measurements revealed no significant differences in the 50% withdrawal threshold among the groups. A significant reduction in withdrawal thresholds was observed at day 7 and was maintained at day 22 in the CIPN group ($p < 0.001$). Fenofibrate administration did not improve the 50% withdrawal threshold on day 7, whereas a significant increase in the 50% withdrawal threshold was observed at day 22 compared with the CIPN + vehicle group. Fig. 2B shows that administration of either oxaliplatin or fenofibrate did not induce changes in body weight in any group.

The effect of fenofibrate on relative IBA-1 mRNA expression in the ACC

The profile of IBA-1 mRNA expression in the ACC is presented in Fig. 3. Oxaliplatin administration increased IBA-1 mRNA expression in the ACC ($p = 0.0121$). Treatment with fenofibrate at 150 mg/kg did not change IBA-1 expression in the ACC. However, 300 mg/kg of fenofibrate appeared to reduce IBA-1 mRNA expression in the ACC ($p = 0.0327$).

The effect of fenofibrate on relative cytokine mRNA expression in the ACC

The mRNA expression profile of the pro-inflammatory cytokine TNF-α in the ACC is shown in Fig. 4. Oxaliplatin administration tended to increase TNF-α mRNA expression in the ACC ($p = 0.0203$). Treatment with fenofibrate at 150 and 300 mg/kg ($p = 0.0374$; $p = 0.0346$) appeared to reduce TNF-α mRNA expression in the ACC of neuropathic model mice.

The effect of fenofibrate on relative caspase-3 mRNA expression in the ACC

Fig. 5 presents the caspase-3 mRNA expression profile in the ACC. Oxaliplatin administration significantly increased caspase-3 expression in the ACC ($p = 0.0074$). Fenofibrate at 150 mg/kg tended to decrease caspase-3 mRNA expression in the ACC ($p = 0.0428$). In contrast, treatment with 300 mg/kg fenofibrate did not alter caspase-3 mRNA expression in the ACC.

Discussion

This study demonstrates that oxaliplatin administration induces peripheral neuropathy. The significant reduction in mechanical withdrawal thresholds observed in oxaliplatin-treated mice reflects the development of mechanical allodynia, which became evident by day 7 and remained present at day 22. Fenofibrate at 150 and 300 mg/kg significantly improved allodynia responses in oxaliplatin-induced neuropathy (Fig. 2A). These findings are consistent with previous studies showing that platinum-based chemotherapeutic agents, such as oxaliplatin, and taxanes, such as paclitaxel, induce neuropathic pain in rodents, and that this effect was ameliorated by fenofibrate administration (Esmaeili et al. 2016; Caillaud et al. 2021; Zhang

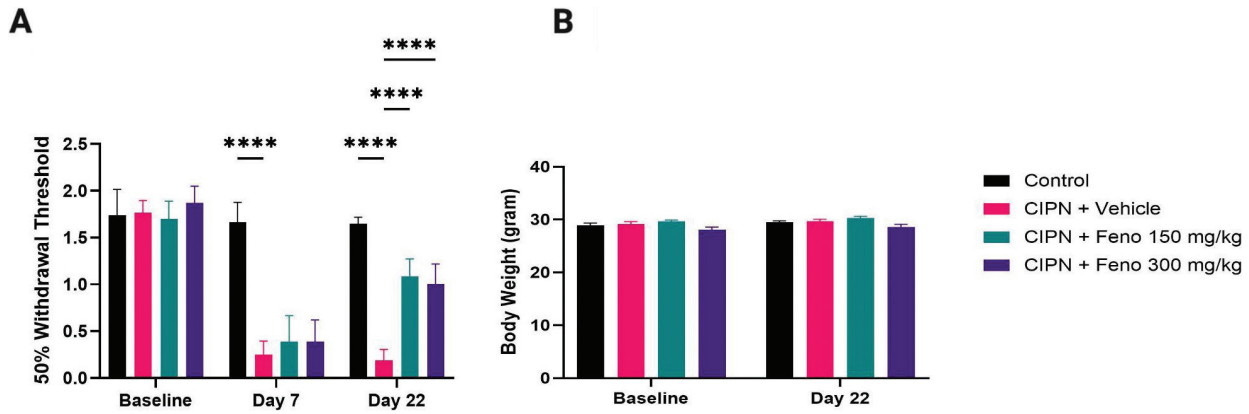

Figure 2. The effect of fenofibrate (Feno) on oxaliplatin-induced allodynia measured using the von Frey test (**A**) and body weight (**B**). Pain thresholds are presented as the 50% withdrawal threshold (g) versus time (days), and body weight is presented as the mean. Values are expressed as mean ± SEM, n = 5. Note: ****– $p < 0.0001$.

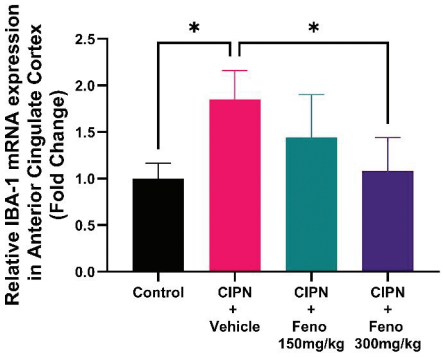

Figure 3. The effect of fenofibrate (Feno) on IBA-1 mRNA expression. Data are presented as mean ± SEM, n = 3–4. Note: * – $p < 0.05$.

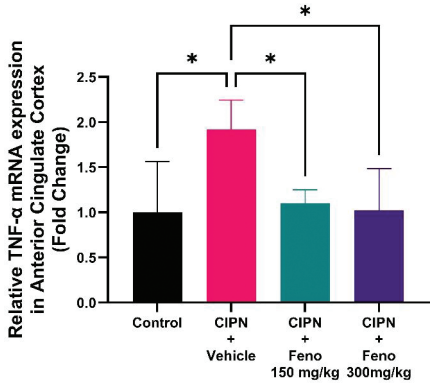

Figure 4. The effect of fenofibrate (Feno) on TNF-α mRNA expression. Data are presented as mean ± SEM, n = 3–4. Note: * – $p < 0.05$.

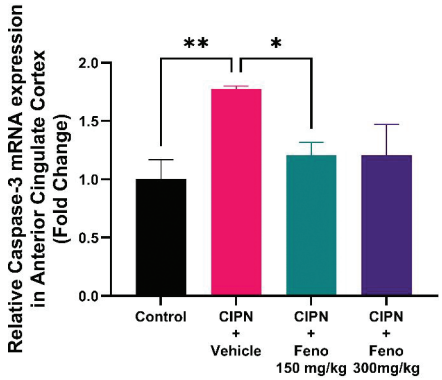

Figure 5. The effect of fenofibrate (Feno) on caspase-3 mRNA expression. Data are presented as mean ± SEM, n = 3–4. Note: * – $p < 0.05$; ** – $p < 0.01$.

et al. 2022a; Aliyah et al. 2023). Co-treatment with fenofibrate has been reported to prevent the development of thermal hyperalgesia in mouse models of CIPN (Aliyah et al. 2023). Mice body weight was measured one day before induction and on the final day before sacrifice. No statistically significant differences in body weight were observed among all groups (Fig. 2B). These findings indicate that oxaliplatin administration did not affect appetite or induce metabolic disturbances, consistent with previous studies (Lee et al. 2012; Park et al. 2015). Furthermore, fenofibrate, as a PPARα agonist, did not exert additional toxic effects on the metabolic status of the mice (Caillaud et al. 2021).

This present study confirms the involvement of the ACC in processing nociceptive signals induced by oxaliplatin. Under neuropathic conditions, microglial activation in the ACC is indicated by a significant increase in IBA-1 mRNA expression (Fig. 3). This finding is consistent with previous research demonstrating increased expression of IBA-1 and GFAP, markers of microglial and astrocytic activation, in SNI animal models (Li et al. 2022). Treatment with fenofibrate at 300 mg/kg significantly reduced IBA-1 mRNA expression. Exposure to toxic compounds such as oxaliplatin can induce mitochondrial dysfunction and oxidative stress, leading to the release of high mobility group box-1 (HMGB1), which promotes the differentiation of microglia into a pro-inflammatory (M1) phenotype (Fumagalli et al. 2021).

The M1 phenotype of microglia releases inflammatory mediators, including pro-inflammatory cytokines, e.g., IL-1β, IL-6, and TNF-α. In this study, relative TNF-α mRNA expression was measured to assess the involvement of this pathway. The results showed that TNF-α mRNA expression was increased in the ACC of the neuropathy group (Fig. 4). Consistent with previous findings, increased IBA-1 and GFAP expression in SNI animal models has been associated with elevated levels of cytokines, e.g., IL-1β, IL-6, and TNF-α, and chemokines, e.g., CCL2 and CXCL1 (Li et al. 2022). Fenofibrate administration at all doses (150 and 300 mg/kg) markedly reduced TNF-α mRNA expression in the ACC. Activation of PPARα by fenofibrate suppresses the NF-κB transcription pathway, thereby inhibiting pro-inflammatory cytokine transcription and promoting a phenotypic shift in microglia to the anti-inflammatory M2 state (Zhou et al. 2022).

This study also explored the neuronal death pathway in the ACC under CIPN conditions. Caspase-3 mRNA expression was notably increased in the neuropathy group (Fig. 5), with previous research reporting that peripheral nerve injury in mice significantly reduced the number of neurons in the ACC. The activation of caspase-3 in the ACC was documented in SNI mouse models (Tan et al. 2018). The increased expression of caspase-3 mRNA is most likely associated with neuroinflammation. Microglial activation and cytokine signaling trigger oxidative stress, leading to cytochrome c release, which, in turn, activates caspase-9 and caspase-3 to initiate neuronal apoptosis under inflammatory conditions (Huang et al. 2025). Administration of fenofibrate at 150 mg/kg suppressed caspase-3 expression in the ACC (Fig. 5). This result is consistent with previous studies reporting the neuroprotective effects of fenofibrate in protecting neuronal cells from apoptosis (Pearsall et al. 2019; Hsu et al. 2020; Oshitari 2024). Activation of PPARα by fenofibrate reduces oxidative stress and mitochondrial dysfunction, thereby suppressing the activation of pro-apoptotic proteins, ultimately protecting cells from programmed cell death (Hsu et al. 2020). The comprehensive molecular mechanism underlying PPAR-α activation in the modulation of neuroinflammation in the anterior cingulate cortex is illustrated in Fig. 6.

This study provides new insights into the protective effects of fenofibrate in the ACC under neuropathic

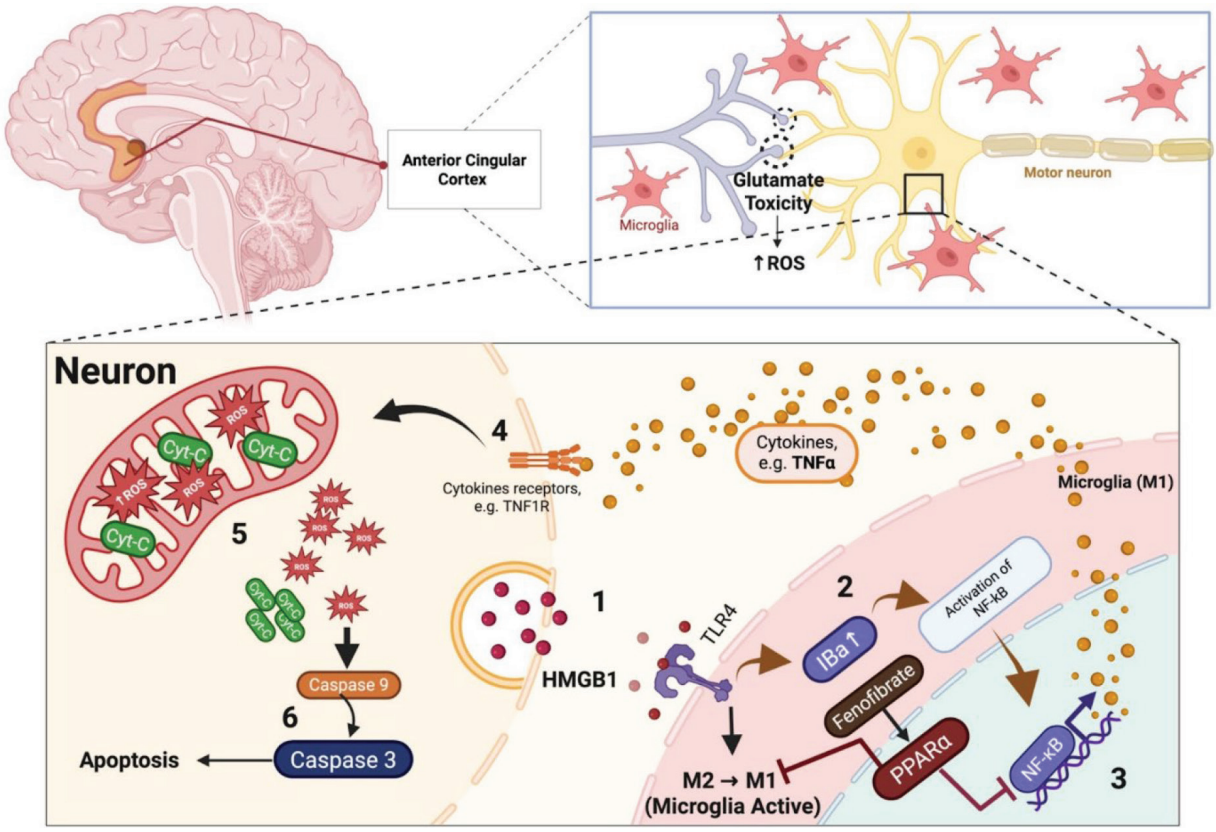

Figure 6. Schematic mechanism by which fenofibrate attenuates neuroinflammation and neuronal apoptosis in the ACC. Activation of PPARα by fenofibrate suppresses the shift of microglial activation toward the pro-inflammatory M1 phenotype and attenuates NF-κB signaling, a key transcriptional regulator of pro-inflammatory cytokines. By reducing cytokine production, oxidative stress and mitochondrial dysfunction are subsequently limited, thereby inhibiting pro-apoptotic signaling and ultimately protecting cells from programmed cell death (Hsu et al. 2020; Bazzari and Bazzari 2022; Zhang et al. 2022b; Zhou et al. 2022). Abbreviations: ACC, anterior cingulate cortex; PPARα, peroxisome proliferator-activated receptor α; NF-κB, nuclear factor kappa B.

conditions, thereby demonstrating the potential effect of fenofibrate in clinical application as a therapeutic agent for CIPN. Several limitations should be considered, including the modest sample size, the primary focus of molecular analyses on gene expression, and the scope of behavioral assessment. Future studies incorporating complementary protein-level analyses and histological approaches would further strengthen the validation of microglial activation and apoptotic processes in the anterior cingulate cortex.

Conclusion

Fenofibrate treatment was associated with reduced mRNA expression of IBA-1, TNF-α, and caspase-3 in the anterior cingulate cortex, suggesting modulation of neuroinflammation in chemotherapy-induced neuropathic pain.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

Experiments on animals: Animal Ethics Committee of the Faculty of Veterinary Medicine, Airlangga University (Approval No. 2.KEH.023.03.2023).

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Use of AI

No use of AI was reported.

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Author contributions

C.A: conceptualization, methodology, manuscript validation. N.P.I.M.P.K: investigation, writing the original draft. D.A: writing the original draft. A.A.I.E.P., A.N.A: investigation. I.N.B.S: formal analysis. A.S.B., S.S: data curation and validation. D.W.S: manuscript review and editing. J.A.L: manuscript validation. M.R: methodology. J.K: conceptualization.

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Data availability

All of the data that support the findings of this study are available in the main text.

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