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Research Article

Curcumin ameliorates oxaliplatin-induced allodynia response and melanocortin downregulation in the spinal cord

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Abstract

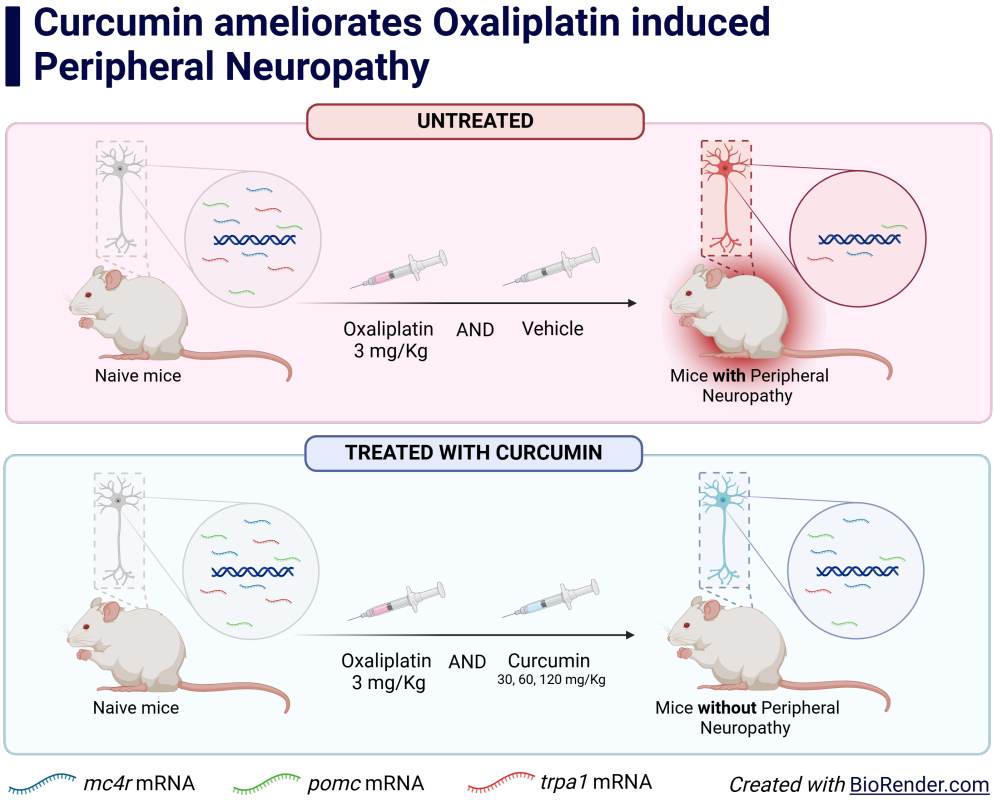
Introduction: Oxaliplatin is a platinum-based chemotherapy agent that often causes chemotherapy-induced peripheral neuropathy (CIPN). This effect limits the potential activity and decreases the cancer patient's quality of life. Melanocortin and transient receptor potential ankyrin 1 (TRPA1) pathways are believed to be essential in recruiting an allodynia response. Based on previous studies, curcumin has shown antioxidant and anti-inflammatory activities that could potentially be useful for decreasing the allodynia effects of oxaliplatin treatment. This study investigated the effect of curcumin on CIPN conditions. In addition, we further elaborated to measure the involvement of spinal melanocortin and the TRPA1 system.

Materials and Methods: A total of 30 male Balb/C mice aged 6-7 weeks old and weighing 20-30 g were used in this study. Mice were injected with oxaliplatin 3 mg/kg four times in the first week of the study. In the second week of the study, curcumin 30, 60, and 120 mg/kg was injected intraperitoneally for 7 days. Allodynia response was measured using the von Frey filament test. Melanocortin 4 receptor (*Mc4r*), Pro-opiomelanocortin (*Pomc*) and *Trpa1* mRNA expressions were measured using RT-qPCR.

Results: Oxaliplatin-induced mechanical allodynia response in mice, characterized by a decrease in the 50% withdrawal threshold parameter, was followed by a significant decrease in the *Mc4r*, *Pomc*, and *Trpa1* mRNA expressions in the spinal cord. Curcumin administration in all doses improves the 50% withdrawal threshold parameter in mice induced by oxaliplatin. Furthermore, curcumin increases the *Mc4r* and *Pomc*, but not the *Trpa1* mRNA expressions in the spinal cord.

Conclusion: Curcumin significantly reduces the allodynia response induced by oxaliplatin. In addition, curcumin ameliorates the melanocortin, but not TRPA1, downregulation in the spinal cord.

Graphical abstract



Keywords

allodynia, cancer, CIPN, curcumin, melanocortin, neuropathy, oxaliplatin, TRPA1

Introduction

Chemotherapy-Induced Peripheral Neuropathy (CIPN) is a peripheral neuropathy caused by chemotherapy agents that damage the peripheral nervous system (Staff et al. 2017; Kim 2020). Administration of platinum-class chemotherapy drugs, such as oxaliplatin or cisplatin, often induces neuropathic pain due to its neurotoxic effects (Di Cesare Mannelli et al. 2014; Lin et al. 2015). This neuropathic pain causes a mechanical allodynia response in the cancer patient. Mechanical allodynia is characterized by a pain sensation due to light stimulus that should not cause pain in normal conditions (Jensen et al. 2014). This condition limits the potential activity and decreases the cancer patient's quality of life (Korczeniewska et al. 2021).

Mitochondrial damage and oxidative stress have been highlighted as major mechanisms in the pathophysiology of neuropathy induced by platinum-class drugs (Zajączkowska et al. 2019; Li et al. 2021). In addition to the mitochondrial damage and oxidative stress, melanocortin and transient receptor potential ankyrin 1(TRPA1) pathways were believed to be essential in recruiting neuropathy response caused by platinum-class drugs (Park et al. 2015; Li et al. 2017). The melanocortin pathway consists of alpha-melanocyte stimulating hormone (α-msh) as an agonist and melanocortin receptor (Sharfman and Gilpin 2021). Previous studies have demonstrated the neuroprotective effect of α-msh produced from the pre-opiomelanocortin (POMC) gene and melanocortin 4 receptor (MC4R) in several diseases such as Alzheimer's and storke (Lau et al. 2021; Ardianto et al. 2023). In addition, MC4R has been determined to play an important role in attenuating neurotoxicity including neuropathic pain cases (Korczeniewska et al. 2021). Besides the melanocortin pathway, TRPA1 was strongly connected with the peripheral neuropathy condition induced by chemotherapy agents (Park et al. 2015; Marcotti et al. 2023). TRPA1 is a cation channel that regulates the physical stimuli and cellular stress product. This channel was found in large populations in the peripheral nerve system such as the spinal cord and dorsal root ganglion (Souza Monteiro de Araujo et al. 2020). In previous study, TRPA1 was found to contribute in the pain perception (Beskhmelnitsyna et al. 2015).

Curcumin is a secondary metabolite from Curcuma

longa that has biological activity, including neuroprotective, anti-inflammatory, and antioxidant activities (Fan et al. 2013). Curcumin has also been reported to exert antinociceptive effects in various animal pain models (Mittal et al. 2009; Waseem and Parvez 2016). Although some evidence of curcumin's effect on neuropathic pain has been published, there is a lack of evidence demonstrating the effect of curcumin in reducing peripheral pain responses associated with the melanocortin and TRPA1 expression in the spinal cord. Thus, this study investigates the effect of curcumin on allodynia response in mice induced by oxaliplatin. In addition, we elaborated further to measure the gene expression of melanocortin and *Trpa1* in the spinal cord.

Materials and Methods

Animals

Male Balb/C mice with aged 6-7 weeks old and weighing 20-30 g were used in this study. The mice were housed in the Animals Laboratory, Faculty of Pharmacy, Universitas Airlangga, Indonesia. The mice were acclimatized for 7 days under the standard condition consisting of a constant temperature (25±1°C) and a 12-hour light/dark cycle. In addition, food and water were given ad libitum. The study has been designed to reduce the number of animals. The animal was only used once and was not involved in another study. All treatments were designed to minimize the animal suffering. A total of 30 mice were divided into 5 groups consisting of control (vehicle-injected), neuropathy (oxaliplatin-injected), neuropathy + curcumin 30 mg/kg, neuropathy + curcumin 60 mg/kg, and neuropathy + curcumin 120 mg/kg. The protocol of this study was approved and conducted according to the animal handling guidelines of the Ethic Committee, Faculty of Veterinary Medicine, Universitas Airlangga, Indonesia, No: 2.KE.052.03.2021.

Drug administration

Oxaliplatin (Sigma-Aldrich, USA) and Curcumin (Tokyo Chemical Industry, Japan) were used in this study. Oxaliplatin was dissolved in a 5% dextrose solution while curcumin was dissolved in 5% Tween 80. Both substances were dissolved immediately prior to injection according to the timeline of the study. The oxaliplatin 3 mg/Kg was injected intraperitoneally on days 0, 1, 3, and 5. The curcumin doses of 30, 60, and 120 mg/kg were injected Intraperitoneally from days 7 to 14. All animals were subcutaneously injected with 10 ml/kg saline 30 minutes after the oxaliplatin administration to prevent kidney injury.

Behavior test

Mice were placed in 12 cm × 8 cm acrylic boxes equipped with a wire-mesh floor. Mice were habituated to the environment for 15-30 min before the test. A series of von Frey filaments were used ranging from 0,02 to 2 g. Punctuate stimulus was delivered to the mid-plantar area of the hind paw from below the wire-mesh floor, starting with a 0.6 g force filament. Stimuli were applied on the mid-plantar of the hind paw at intervals of 30 seconds. Measurements were repeated 5 times for each filament force, and the final value of the withdrawal threshold was obtained through calculation with the Up-Down method. Behavioral test using the von Frey filaments was carried out on days 0, 1, 3, 5, 7, 10, 14, 18, and 22.

RT-qPCR

The mice were sacrificed, and the spinal cord was extracted on day 22. Total RNA was purified using an RNA Purification Kit (Jena Bioscience, Germany). Reverse transcription enzyme (Promega, USA) was used to synthesize the cDNA. The amplification was performed according to standard cycling conditions according to the Gotaq qPCR master mix (Promega, USA). This involved a polymerase activation at 95°C for 2 minutes, followed by 40 cycles of denaturation at 95°C for 15 s, annealing and extension at 60°C for 1 minute. Specific primers used in this study included: *Mc4r* (forward: 5'-ACAGCGAGTCTCAGGGAAAA-3'; reverse 5'-TTGACCAGTCTGCTGTTTGC-3'); *Pomc* (forward: 5'-CGAGGCCTTTCCCCTAGAGT-3'; reverse 5'-CCAGGACTTGCTCCAAGCC-3'); *Trpa1* (forward: 5′-GTACTTCTTGTCGTGTTTCTTGC-3′; reverse 5′-ACCATCGTGTATCCAAATAGACC-3′); B-actin (forward: 5'-TTCTTGGGTATGGAATCCTGT-3'; reverse 5'-AGCACTGTGTTGGCATAGAG-3'). PCR results were processed using the $2^{-\Delta\Delta CT}$ formula.

Statistical analysis

All data were presented as mean ± S.E.M. The data obtained from the test results with von Frey filaments were analyzed using two-way ANOVA followed by a post hoc Bonferroni test. For gene expression results, one-way ANOVA analysis followed by a post hoc LSD test was used. Differences were considered statistically significant at $p<0.05$. All calculations were performed using the GraphPad Prism 9 Software (GraphPad, Inc., San Diego, CA, USA).

Results

Effect of curcumin on the oxaliplatin-induced peripheral neuropathy

Neuropathic pain responses in mice were described by the 50% withdrawal threshold or 50% mechanical threshold value when mice tried to have a certain pain response, such as pulling, licking, or claw movement during the von Frey test. The results (Fig. 1) show that oxaliplatin administration significantly reduces the 50% withdrawal threshold score, which indicates mice suffering mechanical allodynia ($P<0.0001$). The decline in the 50% withdrawal threshold score began on the 5th day ($P=0.0199$) and continued to deteriorate until the 22nd day ($P<0.0001$).

In the present study, the administration of curcumin 30 mg/kg in a neuropathic pain model showed a significant increase in the 50% withdrawal threshold value on day 22 ($P<0.0001$) (Fig. 1). Administration of curcumin 60 mg/kg in a neuropathic pain model showed an increase in 50% withdrawal threshold, which started on day 18 ($P=0.0001$) and then continued to increase until day 22nd ($P<0.0001$). Lastly, curcumin 120 mg/kg administration showed an increase in 50% withdrawal threshold, which started on the 14th day ($P=0.0091$) and continued to increase until the 22nd day ($P<0.0001$). These three results show a correlation between the dose increase and the recovery time from the neuropathic pain caused by oxaliplatin.

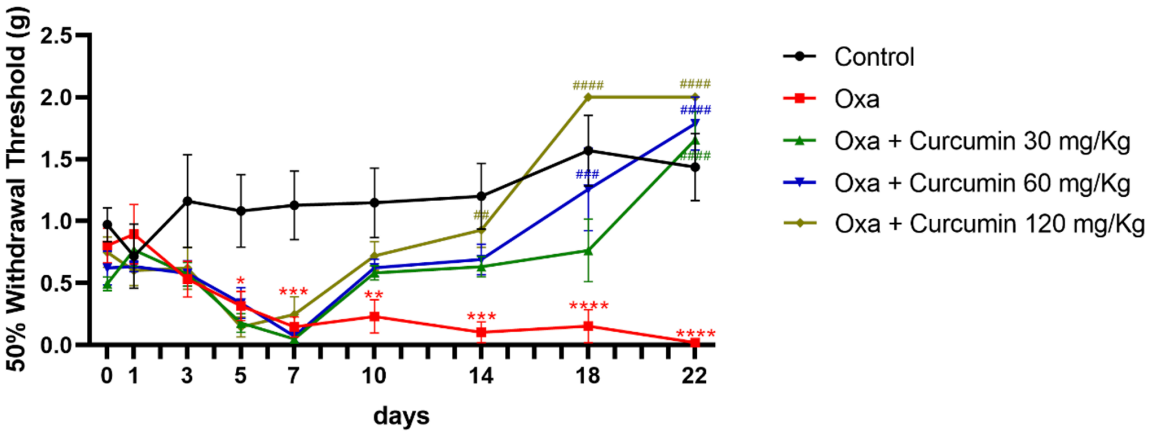


Figure 1. Effect of curcumin on oxaliplatin-induced peripheral neuropathy pain as measured by the von Frey Test. Data were displayed with a profile of 50% Withdrawal Threshold (grams) vs. time (day-). Data were shown as mean ± SEM, n=6. ***Note:*** ** – P<0.01; *** – P<0.005; **** – P<0.001. Oxa – Oxaliplatin.

Effect of curcumin on the melanocortin system in the spinal cord

The melanocortin gene expression profile in the spinal cord was presented in Fig. 2. Oxaliplatin administration significantly reduced *Mc4r* mRNA expression in the spinal cord (P=0.0187). Furthermore, there was a significant increase in *Mc4r* mRNA expression in the spinal cord after curcumin administration (P=0.0401) (Fig. 2A). In line with the *Mc4r* results, *Pomc* mRNA expression in the spinal cord was significantly decreased due to oxaliplatin administration (P=0.0071). Curcumin administration ameliorates the *Pomc* mRNA downregulation in the spinal cord (P=0.0466) (Fig. 2B).

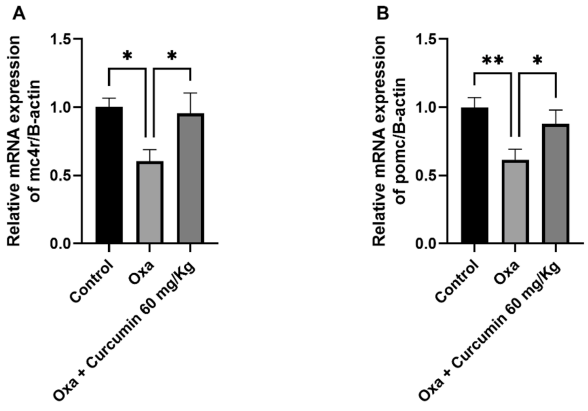


Figure 2. Effect of quercetin on mRNA expression of *Mc4r* (**A**) and *Pomc* (**B**) in the spinal cord. Data were shown as mean ± SEM, n=4-5. ***Note:*** * – P<0.05; ** – P<0.01. Oxa – Oxaliplatin.

Effect of curcumin on Trpa1 mRNA expression in the spinal cord

Trpa1 mRNA expression in the spinal cord is shown in Fig. 3. Oxaliplatin administration resulted in a decrease in *Trpa1* mRNA expression in the spinal cord (P=0.0416). The administration of curcumin did not change the expression of *Trpa1* mRNA in the spinal cord of mice suffering peripheral neuropathy induced by oxaliplatin (P=0.8591).

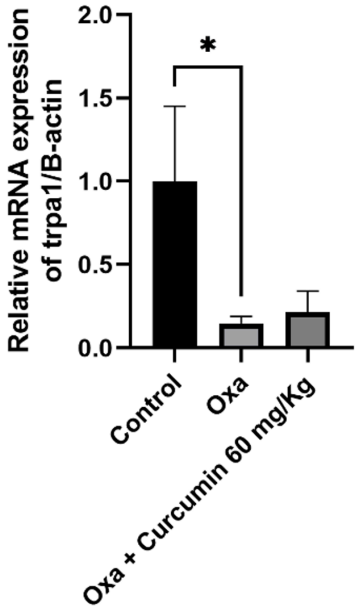


Figure 3. Effect of quercetin on mRNA expression of *Trpa1* in the spinal cord. Data were shown as mean ± SEM, n=6. ***Note:*** * – P<0.05. Oxa – Oxaliplatin.

Discussion

This study demonstrated the neuroprotective effect of curcumin on mechanical allodynia response induced by oxaliplatin. Allodynia response was detected in mice due to oxaliplatin administration. The allodynia response deteriorated until the last day even though the oxaliplatin administration was terminated on the first week of study. This condition shows that the side effects of oxaliplatin were a serious problem. In addition, this result was consistent with previous studies that demonstrated the administration of oxaliplatin-induced neuropathic pain in

rodents by providing cold allodynia, mechanical allodynia, hyperalgesia and hypoesthesia effects (Hopkins et al. 2016; Ardianto et al. 2022). Curcumin in all doses ameliorates the deteriorating effect of oxaliplatin in providing an allodynia response. Interestingly, this study found a correlation between dose increasing and recovery speed in the neuropathic pain condition caused by oxaliplatin. This result was in line with the previous study that demonstrated curcumin at doses of 30 and 60 mg/kg was able to reduce cold allodynia and mechanical hyperalgesia which was examined using the cold plate test and pinprick (Babu et al. 2015).

Melanocortin was considered a pathway that related to the nociception and pain response due to its high population in both the central and peripheral nervous systems. Melanocortin through MC4R modulation was known to have interaction with the serotonergic, glutamatergic and dopaminergic in pain modulation. A study by Starowicz et al. (2004) shows that sciatic nerve injury caused a decrease in *Mc4r* mRNA expression in the dorsal root ganglion. In addition to that result, our study revealed that oxaliplatin induction was able to decrease the *Mc4r* mRNA expression in the spinal cord. Furthermore, a decrease in the *Pomc* mRNA expression in the spinal cord was also observed. A decrease in *Mc4r* mRNA expression was previously correlated with the compensatory state of the allodynia response. This *Mc4r* downregulation limited the pro-allodynic effect of the MC4R agonist (Starowicz et al. 2004).

Oxaliplatin-induced decrease in *Mc4r* and *Pomc* mRNA expressions in the spinal cord was successfully eliminated by curcumin treatment. This result indicates a positive correlation between the effects of curcumin on the anti-allodynia effect and the melanocortin gene expression in the spinal cord. This correlation certainly strengthens the suspicion of the involvement of the melanocortin system in neuropathic pain induced by oxaliplatin. Furthermore, since the neuropathic pain was known to be initiated by MC4R activation, curcumin's ability to reduce *Mc4r* and *Pomc* mRNA expressions suggests that it has a neuroprotective effect (Li et al. 2017). Curcumin was previously revealed to reduce proinflammatory cytokines in the spinal cord and sciatic nerve tissue (Kandhare et al. 2012; Yardim et al. 2021). This activity might be correlated with the curcumin effect on the MC4R since the upregulation of the proinflammatory cytokines was influenced by MC4R through regulation of the p38 MAPK and c-Jun N-terminal kinase signaling pathway (Chu et al 2012; Zhao et al. 2019). In addition to the MC4R, results on the *Pomc* mRNA expression in the present study suggest that presynaptic regulation was also involved in exhibiting the anti-allodynia response. This is supported by evidence of POMC neurons which were found to be distributed in the spinal cord (Padilla et al. 2012).

The present study shows that oxaliplatin administration resulted in a decrease in *Trpa1* mRNA expression in the spinal cord. The decrease in *Trpa1* mRNA expression in the spinal cord possibly indicates the body's compensatory mechanism for peripheral neuropathy condition due to oxaliplatin injection. This was supported by previous studies that show the downregulation of *Trpa1* in the peripheral nervous system due to peripheral nerve injury (Katsura et al. 2006; Caspani et al. 2009; Staaf et al 2009). The administration of curcumin did not change the expression of *Trpa1* mRNA in the spinal cord of mice with peripheral neuropathy induced by oxaliplatin injection. These results possibly indicate the selectivity of the mechanism of action of curcumin which does not provide therapeutic effects through modulation of *Trpa1* mRNA expression.

Conclusion

The present study revealed that oxaliplatin 3 mg/kg induced a mechanical allodynia response in mice. In line with the change of the behavior response, the present study found a downregulation of melanocortin and *Trpa1* mRNA expressions in spinal cord due to oxaliplatin treatment. Oxaliplatin-induced mechanical allodynia response was significantly reduced by curcumin supplementation at doses 30, 60 and 120 mg/kg. In addition, curcumin ameliorates the melanocortin, but not *Trpa1* mRNA downregulation in the spinal cord.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Data availability

All of the data that support the findings of this study are available in the main text. The datasets supporting the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgements

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Author Contributions

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