Methylphenidate Attenuates Signs of Evoked Neuropathic Pain in Animal Model

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Summary

Methylphenidate is a psychostimulant that increases dopamine and noradrenaline levels. Recent studies have shown that methylphenidate potentiates the effect of morphine and together suppress acute and chronic pain. In clinical practice, methylphenidate has been used as a treatment for ADHD and changes of pain threshold have been noted in these patients. The aim of this study was to determine the effect of methylphenidate in an animal model of peripheral neuropathic pain. Neuropathic pain was modeled by the chronic constriction of the sciatic nerve (CCI) in Wistar rats. We evaluated the effect of methylphenidate (1 mg/kg, s.c.) on evoked pain (reflex tests - plantar test, vonFrey test and operant test – thermal place preference) and on spontaneous pain (conditioned place preference). CCI induced thermal, mechanical and cold hyperalgesia/allodynia. Methyphenidate suppressed mechanical and cold hyperalgesia/allodynia, while had no effect on thermal one. Therefore, methylphenidate seems to be a new potential pharmacotherapy for the treatment of neuropathic pain.

Key words

Neuropathic pain • Methyphenidate • Psychostimulants • Pain threshold • Chronic constriction injury

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Introduction

Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system either in the periphery or centrally. Patients with neuropathic pain suffer from complicated symptoms characterized by spontaneous ongoing or shooting pain, evoked pain following noxious (hyperalgesia) or non-noxious stimuli (allodynia) and associated psychological problems [1]. Although neuropathic pain affects approximately 7-10 % of the population, pharmacotherapy is still limited.

Opioids are often used to treat neuropathic pain, but they have negative side effects. One of the most common side effects is sedation. Sedation reduces the quality of life of patients and can also hinder pain control. In fact, it is difficult to find the appropriate dose for adequate pain control while minimizing the sedation effect. Therefore current research is focused to find new effective analgesics as alternatives to opioids. Psychostimulants have been shown to potentiate the analgesic properties of opioids and reduce their side effects (such as improving cognitive function, reducing opioid-induced sedation, etc.). In addition, psychostimulant has been used in clinical practices for the treatment of ADHD, narcolepsy, depression. It is important to note that patients treated with psychostimulants rarely become tolerant to them and very few patients develop psychological dependence [2].

Methylphenidate is a psychostimulant that enhances dopamine and noradrenaline levels by inhibiting reuptake. In addition, methylphenidate can modulate μ opioid receptor activity at sufficiently high doses [3,4]. Methylphenidate has been used for several years in clinical practice in children and adolescents for the treatment of attention deficit hyperactivity disorder (ADHD). Recent studies report that ADHD patients treated with methylphenidate have an elevated pain threshold [5,6]. Several clinical studies have shown that methylphenidate potentiates the analgesic effect of opioid

and reduces sedation of cancer patients. In addition, it has a significant effect on improving the cognitive status of patients. Side effects of methylphenidate have been observed very sporadically (hallucinations, attacks). Despite clinical trials suggesting that methylphenidate improves quality of life in cancer patients, the effect of methylphenidate on pain required further investigation [7,8].

Animal studies have shown that methylphenidate potentiates and prolongs the analgesic effect of morphine in acute pain [9,10] and in chronic inflammatory pain (CFA model) [11].

To the authors´ knowledge, the effect of methylphenidate on peripheral neuropathic pain has not been tested. Therefore, the aim of this study was to evaluate the effect of methylphenidate on evoked and spontaneous pain in an animal model of peripheral neuropathic pain.

Methods

Animals and experimental protocol

The adult female Wistar rats (n=30) weighing 310-415 g were used. All rats were housed (2-3 rats per cage) in a temperature-controlled environment, under a 12 : 12 reversed light-dark cycle, and with free access to a standard diet and tap water ad libitum. All behavioral tests were performed from 8:00 A.M. to 5:00 P.M., i.e. during the animals' dark cycle. The mean temperature was 22±2 °C, and the relative humidity equaled 55±10 %. The acclimation period was 5 days long. The experiment was approved by the Committee for Animal Care and Use of the Third Faculty of Medicine, Charles University, Prague, and conducted according to the guidelines of the Ethics Committee of the International Association for the Study of Pain [12]. Animals were randomly divided into the two groups: chronic constriction injury groups (CCI, n=18) and control groups without the constriction (CTRL, n=12). In the first experiment (CCI+methylphenidate (MP), n=6, CCI+saline, n=6, CTRL, n=6), mechanical and thermal withdrawal threshold of both hind limbs and thermal place preference were measured before and after methylphenidate/saline administration. In the second experiment (CCI, n=6, CTRL, n=6), the place preferences were measured before and after conditioning to MP by the conditioned place preference (CPP) test. The behavioral testing was performed in a blind manner.

Methylphenidate/Saline

Methylphenidate hydrochloride (Sigma Aldrich) was dissolved in saline to the concentration of 1 mg/ml. Methylphenidate (MP) or saline (SA) was injected at a dose of 1 mg/kg or the equivalent volume subcutaneously into the dorsal cervical region.

Animal model of neuropathic pain

Rats were anesthetized with combination of ketamine (100 mg/kg) and xylazine (16 mg/kg) injected intraperitoneally together in a single syringe. The CCI model in rats was carried out according to the study of Bennett and Xie [13]. At mid-thigh level, the left common sciatic nerve was exposed proximal to the trifurcation and gently released without stretching the muscles and nerves. Four ligatures were loosely tied (4-0 chromic gut sutures, Resocat ®) around it and 1 mm apart.

Experiment one: evoked pain testing

Evoked pain was tested using reflex tests and thermal place preference on days 10 and 14 after surgery, because pain threshold changes were showed during the estrous cycle of females [14]. We measured twice with an interval of four days to eliminate the effect of the estrous cycle of females. For analysis, the average value of the two measurements was used.

Reflex tests

Paw withdrawal mechanical threshold (PWT) and paw withdrawal thermal latency (PWL) was evaluated by electric von Frey (Ugo Basile) and by the radiant heat (Plantar test, Ugo Basile), resp. The rats underwent 30 min to acclimate to the environment before each test. PWT, PWL values of each hind limb were measured before and 30 min after MP administration for each behavioral assay. Two (vonFrey test) or three (plantar test) repeat measures were acquired in each rat within a 15-min interval. For analysis, the average value of each limb was used.

Thermal place preference (TPP)

The rats were placed in the middle between two plates (hot and cold plate was set to 45 °C and 10 °C, resp.) and they had free access to both plates. The time spent on the cold plate was automatically recorded during 10 min 1 h before and 30 min after the MP administration.

Experiment two: spontaneous pain testing

Conditional place preference (CPP)

Prior to conditioning until day 10 postoperatively, each rat was habituated by being individually placed in the apparatus 3 times for 15 min with free access to both chambers. Then the time spent in the left and right chambers was measured on day 11 and was considered as a basal preference. The conditioning procedure consisted of two conditioning sessions daily, and lasted 4 days. Rats were conditioned in the chamber for 60 min in the morning (at 9 A.M.) and 60 min in the afternoon (at 4 pm). Left chamber was associated with MP and right chamber was associated with SA without the access to the other chamber. In the afternoon part, alternate substance was applied. Final preference was measured on day 16. As before the conditioning, the rat was placed in the apparatus (between left and right chambers) and the time spent in the left or right chambers was recorded for each rat.

Statistics

Data are expressed as means ± standard error of the mean (SEM). Where data was normally distributed according to the Jarque-Bera test, parametric *t*-test was employed to compare two values (for example: left vs. right limb, limb before administration vs. limb after methylphenidate administration, limb of control group vs. experimental group). Non-parametric Wilcoxon test for dependent variables was used to evaluate thermal and condition place preference within the group. All statistical analyses were carried out by Statistica 6.0 (StatSoft Inc., Tulsa, OK, USA). Statistical difference was considered significant when $p<0.05$.

Results

In rats with CCI, both mechanical and thermal withdrawal threshold of the ligated hind limb was lower compared to the contralateral limb (47.67±3.26 g vs. 88.88±6.3 g, $p<0.001$ and 8.48±0.50 s compared to 12.01±0.62 s, $p<0.001$). After MP, both mechanical and thermal threshold of the ligated limb increased compared to the pre-treatment value (74.09±4.21 g; $p<0.001$ and 9.78±0.37 s; $p=0.04$, resp.), however, only mechanical but not thermal threshold did not differ from that of the contralateral limb (contralateral 81.59±5.82 g; $p=0.3$; but 12.07±0.52 s; $p=0.001$; Figs 1, 2).

In the CTRL group, MP increased the thermal withdrawal latency in both left (before 9.57±0.61 s and after 11.45±0.76 s; $p=0.008$) and right hind limb (before 9.67±0.48 s and after 11.56±0.68 s; $p=0.01$) but had no effect on the mechanical withdrawal threshold of the left (before 61.69±6.5 g and after 55.94±7.66 g; $p=0.58$) and right hind limb (before 64.46±10.51 g and after 59.19±9.92 g; $p=0.72$; Figs 1, 2).

Regarding TPP, rats with CCI spent less time on the colder plate compared to the CTRL group (66.5±9.21 s and 111.25±2.95 s; $p=0.01$; resp.). After MP, time spent on the colder plate increased in the CCI group (216.5±76.19 s; $p=0.002$) and did not differ from that in the CTRL group ($p=0.36$). In the CTRL group, MP had no effect on the time spent on the colder plate (after 81.0±25.33 s; $p=0.2$; Fig. 3).

Regarding CPP, MP did not induce the place preference either in the CTRL or CCI group. Before and after the conditioning, CTRL animals spent in the MP-paired chamber 422±31.89 s and 495.8±41.12 s, resp. $p=0.18$. In the CCI group, the time was 558±43.37 s and 561±25.35 s, respectively, $p=0.95$ (Fig. 4).

Discussion

In this study, we used an administration dose 1 mg/kg of MP because it is the highest dose that does not induce stereotyped behavior in rats and increases the analgesic effects of morphine [10]. We used three types of evoked pain tests: vonFrey test, plantar test and TPP, and one type of spontaneous pain test: CPP. VonFrey and plantar tests are based on spinal reflexes, the TPP and CPP involve supraspinal structures because animals have to make decisions. CCI decreased the mechanical and thermal withdrawal latency of the ligated limb compared to the contralateral limb, and decreased time spent on the cold plate in TPP. These findings are in good agreement with previous studies and they are traditionally interpreted as evidences of the peripheral nerve injury and of the already developed hypersensitivity (thermal, cold and mechanical hyperalgesia/allodynia) [13,15-19]. In our study, MP reversed both the mechanical withdrawal threshold and time spent on the cold plate in TPP after CCI, however, thermal withdrawal latency of the ligated limb remained lower compared to the contralateral one after the MP administration and MP did not induce the place preference in the CPP test in CCI rats. Further, MP increased thermal but not mechanical withdrawal threshold in CTRL animals. It suggests that MP exerts antiallodynic effect during mechanical stimulation and TPP test, whereas it exerts antinociceptive effect using thermal stimulation.

Effect of methylphenidate on mechanical and cold allodynia

To the authors´ knowledge, the antiallodynic effect of MP has not been described yet. Based on the pharmacodynamics of MP, its antiallodynic effect might be attributed to a reduction in norepinephrine (NE) reuptake [20-22]. It has been repeatedly shown that drugs blocking NE reuptake reversed the mechanical threshold in CCI model [23,24] or reversed cold allodynia in oxaliplatin-induced neuropathy [25]. At the same time, it has been shown that CCI leads to dysregulation of the descending antinociceptive system and that NE levels decrease after CCI due to reduced locus coeruleus activity [26,27]. We could speculate that MP normalized NE levels after CCI and therefore reversed the mechanical and cold allodynia in CCI rats.

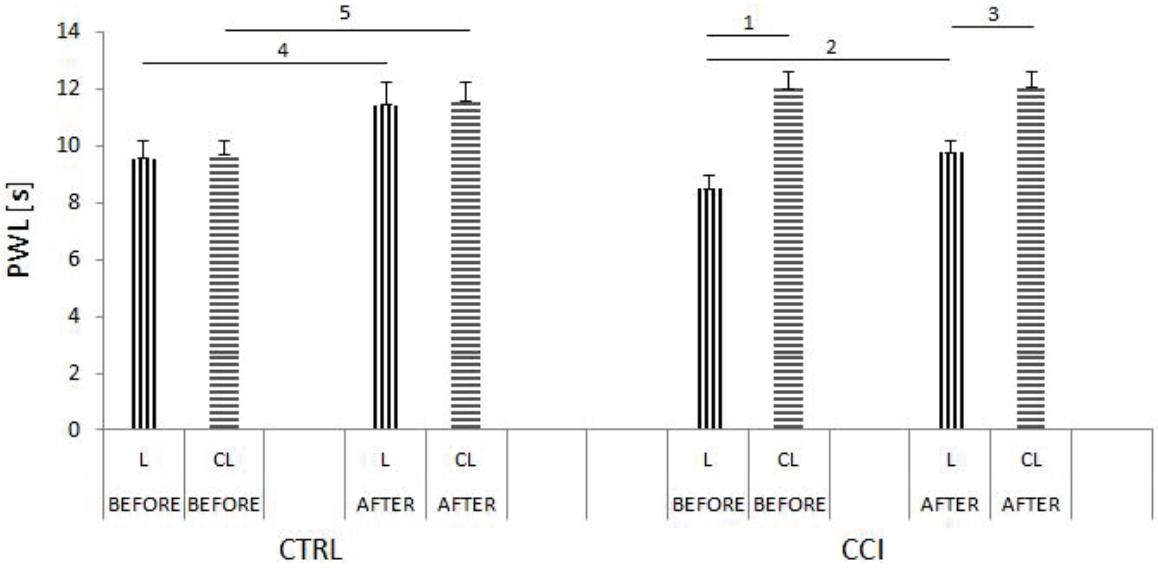

Fig. 1. Paw withdrawal thermal latency (PWL, plantar test). The graph shows the means PWL values of the ligated (L) and contralateral (CL) limbs in CTRL and CCI groups before and after administration of MP. The error bars show SEM and lines show significant difference ($p<0.05$). CCI decreased PWL of the L limb compared to the CL limb of CCI (**1**). MP increased PWL of the L limb in CCI group (**2**), but did not reverse the difference between the L and CL limbs (**3**). MP increased thresholds in both limbs in CTRL group (**4, 5**).

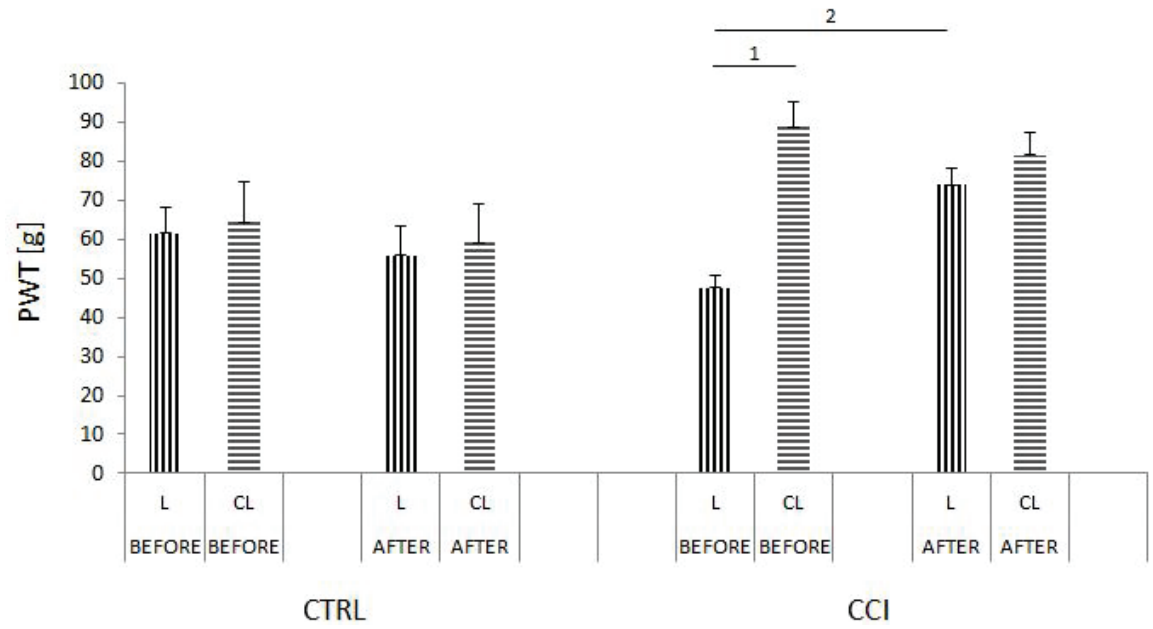

Fig. 2. Paw withdrawal mechanical threshold (PWT, vonFrey test). The graph shows the means PWT values of the ligated (L) and contralateral (CL) limbs in the CTRL and CCI groups before and after administration of MP. The error bars show SEM and lines show significant difference ($p<0.05$). CCI decreased PWT of the L limb compared to the CL limb in CCI (**1**). MP reverse PWT in CCI (**2**). MP had no effect in CTRL.

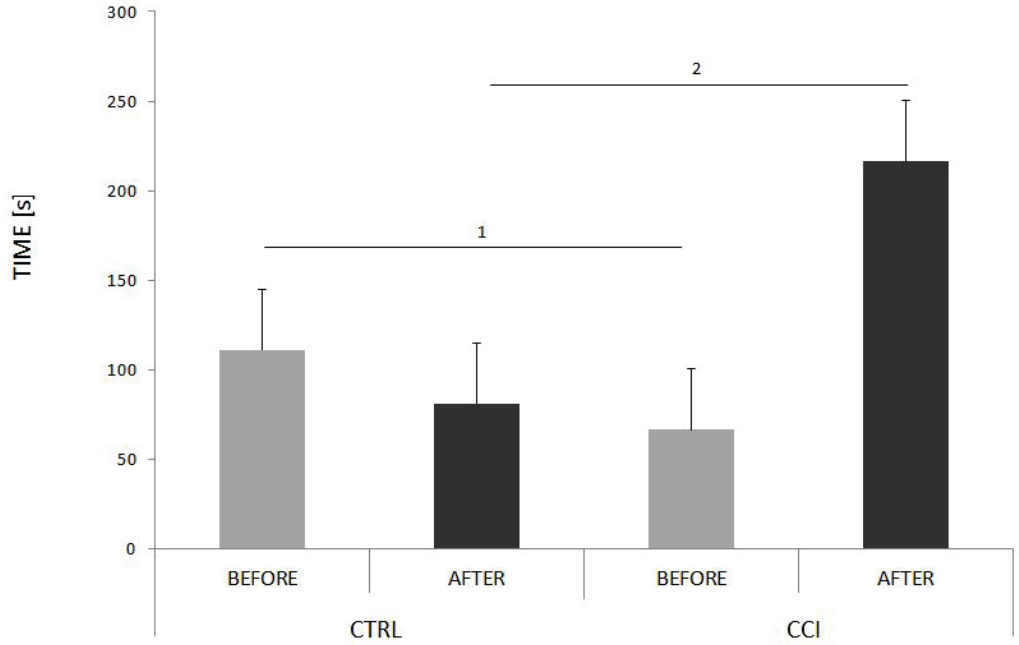

Fig. 3. TPP. The graph shows the time spent on the cold plate before and after administration of MP in CTRL and CCI group. The error bars show SEM and lines show significant difference ($p<0.05$). CCI decreased time spent on cold plate (**1**), MP increased time spent on cold plate (**2**).

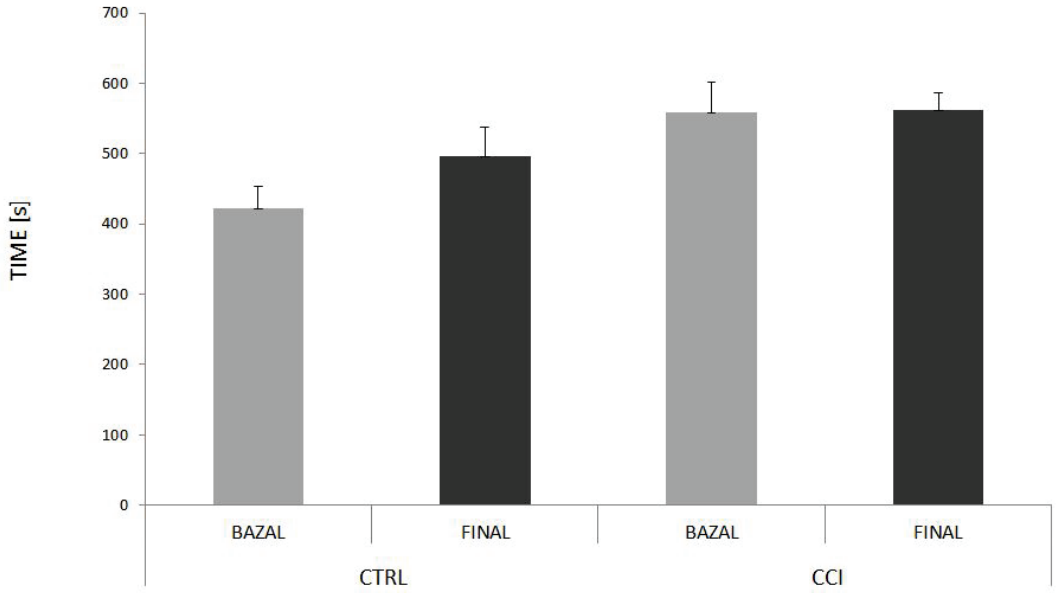

Fig. 4. CPP. The graph shows the time spent in the left chamber before (BAZAL) and after (FINAL) conditioning with MP in CTRL and CCI groups. The error bars show SEM. MP did not induce a preference in CTRL and CCI.

Effect of methylphenidate on thermal hypersensitivity

Different results were obtained by measuring the thermal withdrawal latency of both the CCI and CTRL groups. Although MP increased the thermal withdrawal latency of the ligated limb, the latency was still significantly lower compared to the contralateral limb. In addition, MP increased the thermal withdrawal latency in the CTRL group. This suggests an antinociceptive effect of MP. Indeed, there is extensive evidence that norepinephrine in the spinal cord produces a dose-dependent antinociceptive effect and that norepinephrine-induced antinociception is due to an action on alpha-2-adrenoceptors [28]. However, in this case, an increase in mechanical withdrawal threshold

would also be expected. Therefore, we hypothesize that the dose of MP we used is too low to induce antinociception and that the results of the plantar test could be affected by a change in skin temperature, because monoamines induce a decrease in skin temperature in humans [29,30] and the thermal withdrawal latency is inversely proportional to skin temperature [31]. To answer the question of the effect of MP on skin temperature in rats, we administered MP to three rats and found that skin temperature decreased significantly at an interval of 20-40 min after injection (data not shown). Thus, it is unclear whether the plantar test is a suitable method for assessing the nociception of drugs that alter skin temperature.

Effect of methylphenidate on spontaneous pain

In the second experiment, MP it did not induce preference in CTRL group although it increases dopamine levels and thus stimulates the reward center in the brain [32-34]. In agreement with our results is the finding of Cummins *et al.* [35], who used the same administration dose of MP (1 mg/kg), and preference was also not induced. Sellings *et al.* [36] also did not induced a preference for MP at a dose of 2 mg/kg, while higher administration doses of 3 mg/kg [37] and 5 mg/kg [35,36] induced preference. We can summarize that the induction of preference is dose-dependent. Thus, the administration dose we used is too low to induce a significant reward effect.

MP did not induce preference even in the CCI group. This could be explained by the absence of effect of MP on spontaneous pain. No one has tested the effect of MP in CCI animals using the CPP method. In animals, spontaneous pain is often assessed by a measure of locomotor activity. You *et al.* [11] showed that a dose of 0.25 mg/kg MF did not affect the locomotor activity in rats with chronic inflammatory pain.

An alternative interpretation could be the absence of spontaneous pain in this model. The original study by Bennett and Xie [13] and many others described sudden lifting, increased grooming, different posture of the ipsilateral limb, and slowing of weight gain as signs of spontaneous pain. In disagreement, a study by Dalm *et al.* [38] reported that the CCI neuropathic pain model does not have a spontaneous pain component and therefore should not be used to evaluate the effect of neuropathic pain treatment. In his study, preference was not induced after conditioning in CPP with local anesthetic in CCI rats. Dalm *et al.* [38] also showed that spontaneous spinal cord horn neuron activity in CCI rats did not differ from controls. The absence of spontaneous pain in CCI model was also demonstrated in a 16-day study of CCI mice. The study was focused on quality of life and showed no differences in feeding, drinking and physical activity between the CTRL group and the CCI group. These results support the theory that CCI can develop just hypersensitivity (hyperalgesia and allodynia) and does not have a spontaneous pain component. Therefore, the animal model of CCI could not fully correlate with neuropathic pain in human patients [39]. The presence of spontaneous pain in CCI model is not obvious. Our results showed that either spontaneous pain is absent in CCI model or is not affected by MF.

In this study, we showed, that methylphenidate suppresses mechanical and cold allodynia. Therefore, it could be a potential drug for the treatment of neuropathic pain.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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References

1. The International Association for the Study of Pain. 2018, IASP Terminology. Accessed 28 March 2023. https://www.iasp-pain.org/
2. Reissig JE, Rybarczyk AM. Pharmacologic Treatment of Opioid-Induced Sedation in Chronic Pain. Ann Pharmacother 2005;39:727-731. https://doi.org/10.1345/aph.1E309
3. Halladay LR, Iniguez SD, Furquan F, Previte MC, Chisum AM, Crawford CA. Methylphenidate potentiates morphine-induced antinociception, hyperthermia, and locomotor activity in young adult rats. Pharmacol Biochem Behav 2009;92:190-196. https://doi.org/10.1016/j.pbb.2008.11.011
4. Zhu J, Spencer TJ, Liu-CHen LY, Biederman J, Bhide PG. Methylphenidate and μ opioid receptor interactions: A pharmacological target for prevention of stimulant abuse. Neuropharmacology 2011;61:283-292. https://doi.org/10.1016/j.neuropharm.2011.04.015

5. Treister R, Eisenberg E, Demeter N, Pud D. Alterations in Pain Response are Partially Reversed by Methylphenidate (Ritalin) in Adults with Attention Deficit Hyperactivity Disorder (ADHD). Pain Pract 2013;15:4-11. https://doi.org/10.1111/papr.12129
6. Pud D, Broitman E, Hameed O, Suzan E, Aviram J, Haddad M, Hadad S, Shemesh R, Eisenberg E. Methylphenidate attenuates the response to cold pain but not to aversive auditory stimuli in healthy human: a double-blind randomized controlled study. PAIN Rep 2017;2:e593. https://doi.org/10.1097/PR9.0000000000000593
7. Bruera E, Chadwick S, Brenneis C, Hanson J, Macdonald RN. Methylphenidate associated with narcotics for the treatment of cancer pain. Cancer Treat Rep 1987;71:67-70.
8. Bruera E, Miller MJ, Macmillan K, Kuehn N. Neuropsychological effects of methylphenidate in patients receiving a continuous infusion of narcotics for cancer pain. Pain 1992;48:163-166. https://doi.org/10.1016/0304-3959(92)90053-E
9. Dalal S, Melzack R. Psychostimulant Drugs Potentiate Morphine Analgesia in the Formalin Test. J Pain Symptom Manage 1998;16:230-239. https://doi.org/10.1016/S0885-3924(98)00085-2
10. Yamamotova A, Fricova J, Rokyta R, Šlamberova R. The Effect of Combined Treatment of Opioids With Methylphenidate on Nociception in Rats and Pain in Human. Physiol Res 2016;65(Suppl 5):S567-S575. https://doi.org/10.33549/physiolres.933535
11. You Z, Ding W, Doheny JT, Shen SS, Yang J, Yang L, Chen L, Zhu S, Mao J. Methylphenidate and Morphine Combination Therapy in a Rat Model of Chronic Pain. Anesth Analg 2020;130:518-524. https://doi.org/10.1213/ANE.0000000000004273
12. Zimmermann M. Ethical guidelines for investigations of experimental pain in conscious animals. Pain 1983;16:109-110. https://doi.org/10.1016/0304-3959(83)90201-4
13. Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain 1988;33:87-107. https://doi.org/10.1016/0304-3959(88)90209-6
14. Ibironke GF, Aji KE. Pain threshold variations in female rats as a function of the estrus cycle. Niger J Physiol Sci 2011;26:67-70.
15. De Vry J, Kuhl E, Franken-Kunkel P, Eckel G. Pharmacological characterization of the chronic constriction injury model of neuropathic pain. Eur J Pharmacol 2004;491:137-148. https://doi.org/10.1016/j.ejphar.2004.03.051
16. Gabay E, Tal M. Pain behavior and nerve electrophysiology in the CCI model of neuropathic pain. Pain 2004;110:354-360. https://doi.org/10.1016/j.pain.2004.04.021
17. Vierck CJ, Acosta-Rua AJ, Johnson RD. Bilateral Chronic Constriction of the Sciatic Nerve: A Model of Long-term Cold Hyperalgesia. J Pain 2005;6:507-517. https://doi.org/10.1016/j.jpain.2005.03.003
18. Salte K, Lea G, Franěk M, Vaculín S. Baclofen Reversed Thermal Place Preference in Rats With Chronic Constriction Injury. Physiol Res 2016;65:349-355. https://doi.org/10.33549/physiolres.933008
19. Caporoso J, Moses M, Koper K, Tillman TS, Jiang L, Brandon N, Chen Q, Tang P, Xu Y. A Thermal Place Preference Test for Discovery of Neuropathic Pain Drugs. ACS Chem Neurosci 2020;11:1006-1012. https://doi.org/10.1021/acschemneuro.0c00013
20. Kuczenski R, Segal DS. Effects of Methylphenidate on Extracellular Dopamine, Serotonin, and Norepinephrine: Comparison with Amphetamine. J Neurochem 1997;68:2032-2037. https://doi.org/10.1046/j.1471-4159.1997.68052032.x
21. Volkow ND, Fowler JS, Wang G, Ding Y, Gatley SJ. Mechanism of action of methylphenidate: Insights from PET imaging studies. J Atten Disord 2002;6(Suppl 1):S31-S43. https://doi.org/10.1177/070674370200601S05
22. Wilens TE. Effects of Methylphenidate on the Catecholaminergic System in Attention-Deficit/Hyperactivity Disorder. J Clin Psychopharmacol 2008;28(3 Suppl 2):S46-S53. https://doi.org/10.1097/JCP.0b013e318173312f
23. Nielsen CK, Lewis RJ, Alewood D, Drinkwater R, Palant E, Patterson M, Yaksh TL, McCumber D, Smith MT. Anti-allodynic efficacy of the χ-conopeptide, Xen2174, in rats with neuropathic pain. Pain 2005;118:112-124. https://doi.org/10.1016/j.pain.2005.08.002
24. Murai N, Aoki T, Tamura S, Sekizawa T, Kakimoto S, Tsukamoto M, Oe T, ET AL. AS1069562, the (+)-isomer of indeloxazine, exerts analgesic effects in a rat model of neuropathic pain with unique characteristics in spinal monoamine turnover. J Pharmacol Exp Ther 2014;348:372-382. https://doi.org/10.1124/jpet.113.208686

25. Balayssac D, Ling B, Ferrier J, Pereira B, Eschalier A, Authier N. Assessment of thermal sensitivity in rats using the thermal place preference test. Behav Pharmacol 2014;25:99-111. https://doi.org/10.1097/FBP.0000000000000026
26. Alba-Delgado C, Cebada-Aleu A, Mico JA, Berrocoso E. Comorbid anxiety-like behavior and locus coeruleus impairment in diabetic peripheral neuropathy: A comparative study with the chronic constriction injury model. Prog Neuropsychopharmacol Biol Psychiatry 2016;71:45-56. https://doi.org/10.1016/j.pnpbp.2016.06.007
27. Andreoli M, Marketkar T, Dimitrov E. Contribution of amygdala CRF neurons to chronic pain. Exp Neurol 2017;298:1-12. https://doi.org/10.1016/j.expneurol.2017.08.010
28. Pertovaara, A. Noradrenergic pain modulation. Prog Neurobiol 2006;80:53-83. https://doi.org/10.1016/j.pneurobio.2006.08.001
29. Zahn TP. Minimal Brain Dysfunction, Stimulant Drugs, and Autonomic Nervous System Activity. Arch Gen Psychiatry 1975;32:381-387. https://doi.org/10.1001/archpsyc.1975.01760210115009
30. Mendelson J, Uemura N, Harris D, Nath RP, Fernandez E, Jacob P 3rd, Everhart ET, Jones RT. Human pharmacology of the methamphetamine stereoisomers. Clin Pharmacol Ther 2006;80:403-420. https://doi.org/10.1016/j.clpt.2006.06.013
31. Voděrová L, Šandera Š, Drobil T, Plevová B, Vaculín Š. Skin temperature contribution to the decrease in withdrawal latency following chronic constriction injury. Physiol Behav 2020;227:113147. https://doi.org/10.1016/j.physbeh.2020.113147
32. Volkow ND, Wang GJ, Fowler JS, Ding YS. Imaging the effects of methylphenidate on brain dopamine: new model on its therapeutic actions for attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57:1410-1415. https://doi.org/10.1016/j.biopsych.2004.11.006
33. Engert V, Pruessner J. Dopaminergic and Noradrenergic Contributions to Functionality in ADHD: The Role of Methylphenidate. Curr Neuropharmac 2008;6:322-328. https://doi.org/10.2174/157015908787386069
34. Broussard E, Reyes-Vazquez C, Dafny N. Methylphenidate dose-response behavioral and neurophysiological study of the ventral tegmental area and nucleus accumbens in adolescent rats. Eur J Neurosci 2019;50:2635-2652. https://doi.org/10.1111/ejn.14402
35. Cummins ED, Griffin SB, Burgess KC, Peterson DJ, Watson BD, Buendia MA, Stanwood GD, Brown RW. Methylphenidate place conditioning in adolescent rats: An analysis of sex differences and the dopamine transporter. Behav Brain Res 2013;257:215-223. https://doi.org/10.1016/j.bbr.2013.09.036
36. Sellings LHL, Mcquade LE, Carke PBS. Characterization of dopamine-dependent rewarding and locomotor stimulant effects of intravenously-administered methylphenidate in rats. Neuroscience 2006;141:1457-1468. https://doi.org/10.1016/j.neuroscience.2006.04.040
37. Wooters TE, Walton W, Bardo MT. Oral methylphenidate establishes a conditioned place preference in rats. Neurosci Lett 2011;487:293-296. https://doi.org/10.1016/j.neulet.2010.10.040
38. Dalm BD, Reddy CG, Howard MA, Kang S, Brennan TJ. Conditioned place preference and spontaneous dorsal horn neuron activity in chronic constriction injury model in rats. Pain 2015;156:2562-2571. https://doi.org/10.1097/j.pain.0000000000000365
39. Urban R, Scherrer G, Goulding EH, Tecott LH, Basbaum AI. Behavioral indices of ongoing pain are largely unchanged in male mice with tissue or nerve injury-induced mechanical hypersensitivity. Pain 2011;152:990-1000. https://doi.org/10.1016/j.pain.2010.12.003