Research in Pharmaceutical Sciences, June 2021; 16(3): 286-293
Received: 25-04-2020
Peer Reviewed: 01-07-2020
Revised: 03-10-2020
Accepted: 03-02-2021
Published: 12-05-2021

School of Pharmacy & Pharmaceutical Sciences
Isfahan University of Medical Sciences

Original Article

Effects of valsartan on morphine tolerance and dependence in rats

Ayat Kaeidi[1,2], Morteza Amirteimoury[3], Mohammad-Saleh Zare[3], Amirhossein Nazari[3], Elham Hakimizadeh[1], Jalal Hassanshahi[1,2], and Iman Fatemi[4,*]

[1]Physiology-Pharmacology Research Center, Research Institute of Basic Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, I.R. Iran.
[2]Department of Physiology and Pharmacology, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, I.R. Iran.
[3]Student Research Committee, Rafsanjan University of Medical Sciences, Rafsanjan, I.R. Iran.
[4]Research Center of Tropical and Infectious Diseases, Kerman University of Medical Sciences, Kerman, I.R. Iran.

Abstract

Background and purpose: Opiates are traditionally used for the treatment of pain. Chronic consumption of opiates such as morphine (MOR) induces tolerance and dependence. This study aimed to investigate the effects of valsartan (VAL), as an angiotensin II receptor blocker, on the induction and expression of MOR analgesic tolerance and physical dependence in rats.
Experimental approach: MOR 10 mg/kg was injected s.c. twice a day for 7 days to induce tolerance and dependence. For evaluating the effect of VAL on the induction of MOR analgesic tolerance and physical dependence, 20 mg/kg VAL was administered orally (once a day) during the 7 days of the examination period. The tail-flick test was performed every day. On day 7, 5 mg/kg naloxone () was injected s.c. into the morphine-dependent rats and the rats were monitored for 30 min for the frequency of withdrawal signs such as jumping, diarrhea, defecation, head tremor, rearing, scratching, sniffing, teeth chattering, and wet-dog shake. For evaluating the effect of VAL on the expression of MOR-analgesic tolerance and physical dependence, 45 min before the last MOR injection, VAL was administered only on day 7. The tail-flick test was performed and naloxone was injected into the addicted rats and they were monitored for 30 min for the frequency of withdrawal signs such as jumping, diarrhea, defecation, head tremor, rearing, scratching, sniffing, teeth chattering, and wet-dog shake.
Findings/Results: Our results revealed that the co-administration of VAL with MOR for 7 consecutive days reduced the induction of MOR tolerance. Moreover, VAL administration for 7 days along with MOR reduced the frequency of diarrhea and defecation in naloxone-injected animals.
Conclusion and implications: According to the results presented in this study, chronic administration of VAL prevented the induction of MOR-analgesic tolerance and dependence in rats.

Keywords: Morphine; Physical dependence; Rat; Tolerance; Valsartan.

INTRODUCTION

Morphine (MOR) as an opioid drug has been used for the treatment of acute and chronic pain (1). The most important problem of the long-term consumption of MOR is analgesic tolerance and physical dependence (2). In MOR tolerance, the analgesic effects of MOR decline due to the repetitive administration (3). In order to reach the analgesic effect, increasing the administrative dose is necessary (4). In MOR dependence, if the consumption is ceased abruptly the withdrawal signs will appear (5). Mood disorders, back and leg pain, disturbances of sleep, fatigue, and restlessness are the most important MOR-withdrawal signs (6).

Access this article online

Website: http://rps.mui.ac.ir

DOI: 10.4103/1735-5362.314827

*Corresponding author: I. Fatemi
Tel: +98-9133431737, Fax: +98-3432112794
Email: i.fatemi@kmu.ac.ir

Thus far, the precise underlying mechanisms of these phenomena are not clear but several of the involved mechanisms include the down-regulation of receptors (7), overproduction of free radicals in the central nervous system (CNS) (8), induction of the inflammation in CNS (9), and activation of the N-methyl-D-aspartate (NMDA) receptor and protein kinase C (4). There is no standard treatment for MOR-analgesic tolerance and physical dependence. Therefore, the tolerance and dependence induced by MOR are real challenging conditions that can restrict the use of this beneficial drug (10).

Sartan agents such as valsartan (VAL) as angiotensin II receptor blockers (ARBs) are wildly prescribed for the treatment of hypertension and renal disease (11). These drugs selectively inhibit the angiotensin II type 1 receptor (AT1) (12). Recently, it has been demonstrated that sartans have neuroprotective effects (13,14). These effects have been shown in different animal models such as stroke and traumatic brain injury models through reducing oxidative stress, inflammation, and apoptosis (13-15). It has been reported that another sartan called losartan attenuates the memory impairments in Alzheimer's disease (14). VAL increases the activities of antioxidant defense enzymes such as superoxide dismutase and catalase as well as decreasing the oxidative stress indices such as malondialdehyde in the brain (12). On the other hand, it is well-established that angiotensin II can enhance the release of glutamate, and blocking the AT1 receptor increases the down-regulation of NMDA receptors (16,17). Moreover, it has been found that reducing the production of angiotensin II by captopril can reduce the withdrawal signs and self-administration of MOR as well as morphine-induced conditioned place preference in rats (18-20). In another study, the acute effect of losartan on MOR analgesia was investigated and it was revealed that losartan did not alter the MOR-analgesia response in nonaddicted animals (21).

To the best of our knowledge, there is no report on the role of the AT1 receptor in MOR tolerance and dependence. Regarding the longer half-life, more potency, and higher selectivity of the AT1 receptor of VAL (13), this study was designed to evaluate the efficacy of VAL in the induction and expression of MOR-induced tolerance and dependence in rats.

MATERIALS AND METHODS

Animals

A total of 48 male Wistar rats (250 ± 20 g) were used in this study. The rats were obtained from the animal house of Rafsanjan University of Medical Sciences. They were housed in groups of 3 rats per plastic cage, maintained under a 12/12-h light/dark cycle (lights on from 7:00 to 19:00) with free access to food and water, and kept at 23 ± 2.0 °C. All the experimental procedures were carried out in accordance with the guidelines for the care and use of laboratory animals in Rafsanjan University of Medical Sciences (Ethic No. IR.RUMS.REC.1399.043) and the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Drugs

MOR was obtained from Temad Company (Iran). Naloxone was obtained from Tolidaru Company (Iran). VAL was purchased from Sigma-Aldrich (Germany; Cat. Number: 1708762). All drugs were dissolved in saline.

Induction of MOR tolerance and dependence

MOR tolerance and dependence were induced in rats by repeated s.c. injection of 10 mg/kg drug twice a day (7:00 and 19:00) for 7 consecutive days (5).

Tail flick test

For evaluating the MOR analgesic effect, we used a tail-flick analgesia meter apparatus (UGO BASILE, Italy). Briefly, the tail-flick apparatus was set to create a light beam that focused on the ventral part of the animal’s tail. Tail-flick latency was considered as the time between tail exposure to radiant heat and tail withdrawal. The cut-off time was 10 s to avoid tissue damages. The rats were lightly restrained in a Plexiglas rat restrainer box during the test. The results are expressed as the

percentage of the maximum possible effect (%MPE) which was calculated according to the following equation:

$$MPE\ (\%) = \frac{T1 - T0}{T2 - T0} \times 100$$

where, T_0 is the pre-treatment latency; T_1, the post-treatment latency; and T_2, the cut-off time.

Assessment of the effects of VAL on the induction of MOR tolerance and dependence

For evaluating the effects of VAL on the induction of MOR tolerance and dependence, 20 mg/kg VAL (22) was administered orally once a day during the 7 days of the examination. MOR tolerance was evaluated by the tail-flick test on every experimental day.

Moreover, MOR dependence was assessed following i.p. administration of 5 mg/kg naloxone 2 h after the last dose of MOR on the 7th day. Each rat was placed in a Plexiglas box (35 × 35 × 45 cm) and the frequency of withdrawal signs such as jumping, diarrhea, defecation, head tremor, rearing, scratching, sniffing, teeth chattering, and wet-dog shake was recorded during 30 min (5).

Assessment of the effects of VAL on the expression of MOR tolerance and dependence

For evaluating the effects of VAL on the expression of MOR tolerance and dependence, we used the animals that had received only MOR for 7 consecutive days. 20 mg/kg VAL was administered orally once a day only on the 7th day, 45 min before the last dose of MOR. MOR tolerance was evaluated by the tail-flick test, 30 min after the last dose of MOR.

Moreover, MOR dependence was evaluated following i.p. administration of 5 mg/kg naloxone 2 h after the last dose of MOR on the 7th day. Each rat was placed in a Plexiglas box (35 × 35 × 45 cm) and the frequency of withdrawal signs such as jumping, diarrhea, defecation, head tremor, rearing, scratching, sniffing, teeth chattering, and wet-dog shake was recorded during 30 min (5).

Statistical analysis

Data are expressed as mean ± SEM. Statistical analysis was performed *via* GraphPad Prism version 6.01 for Windows (GraphPad Software, USA). For evaluating the induction of morphine tolerance, we used a two-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test. For evaluating the expression of morphine tolerance and the jumping and other signs of withdrawal, we used Kruskal-Wallis followed by Dunn's multiple comparisons test. *P*-values less than 0.05 were considered statistically significant.

RESULTS

Effects of VAL on the induction and expression of MOR tolerance

Chronic VAL administration did not cause a significant change in the analgesic effect compared with the control animals (Fig. 1). Based on these results, we can exclude the effect of VAL on %MPE. Our results exhibited that the repeated injections of MOR reduced the nociception response which confirmed the induction of MOR analgesic tolerance. Moreover, co-administration of VAL with MOR significantly increased the analgesic latency on days 5 to 7 ($P < 0.01$ for days 5 and 7, $P < 0.05$ for day 6) which indicated that VAL could prevent the induction of MOR analgesic tolerance.

In order to assess the effect of VAL on the expression of MOR tolerance, we administered VAL only once 45 min before the last dose of MOR on the 7th day of the experiment in the animals that had received only MOR. Acute VAL administration did not cause a significant change in the analgesic effects compared with the control animals (Fig. 2). Moreover, the data indicated that acute co-administration of VAL with MOR could not reduce the MOR analgesic tolerance expression.

Effects of VAL on the induction and expression of MOR dependence

The animals in the control and VAL groups showed no withdrawal jumps, whereas the MOR-administered animals exhibited the withdrawal signs which confirmed the induction of MOR dependence (Fig. 3). Moreover, co-administration of VAL with MOR significantly decreased the frequency of defecation and diarrhea which indicated that VAL could prevent the induction of MOR dependence (all $P < 0.05$).

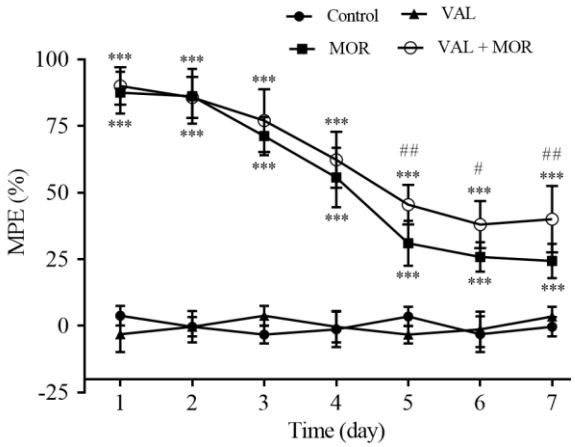

Fig. 1. The effect of chronic treatment with VAL (20 mg/kg) on MOR tolerance induction. Data are expressed as mean ± SEM (n = 6). ***$P < 0.001$ indicates significant differences compared with the control group; $^{\#}P < 0.05$ and $^{\#\#}P < 0.01$ versus the MOR-treated group. MOR, Morphine; MPE, maximum possible effect; VAL, valsartan.

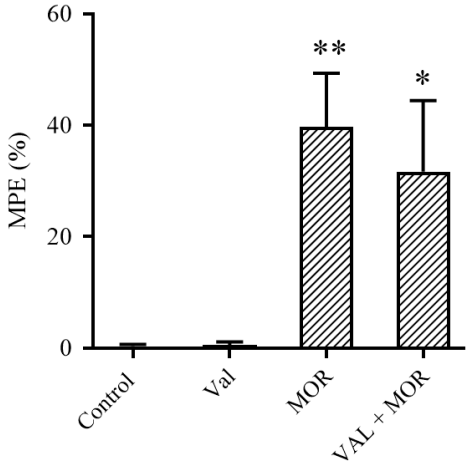

Fig. 2. The effect of acute treatment with VAL on MOR tolerance expression. Data are expressed as mean ± SEM (n = 6). *$P < 0.05$ and **$P < 0.01$ indicate significant differences compared with the control group. MOR, Morphine; MPE, maximum possible effect; VAL, valsartan.

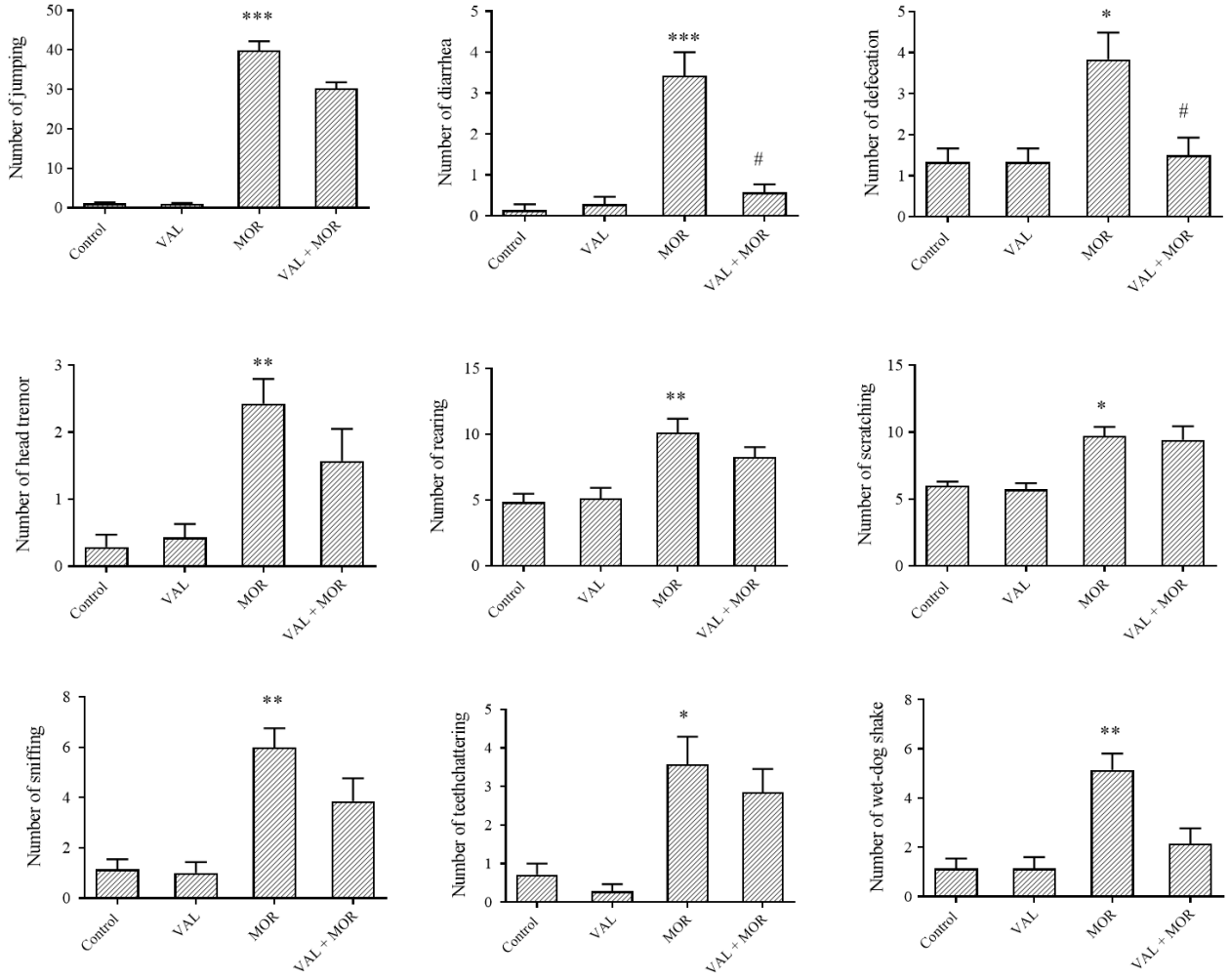

Fig. 3. The effect of chronic treatment with VAL (20 mg/kg) on MOR dependence induction. Data are expressed as mean ± SEM (n = 6). *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ show significant differences compared with the control group; $^{\#}P < 0.05$ versus the MOR-treated group. MOR, Morphine; VAL, valsartan.

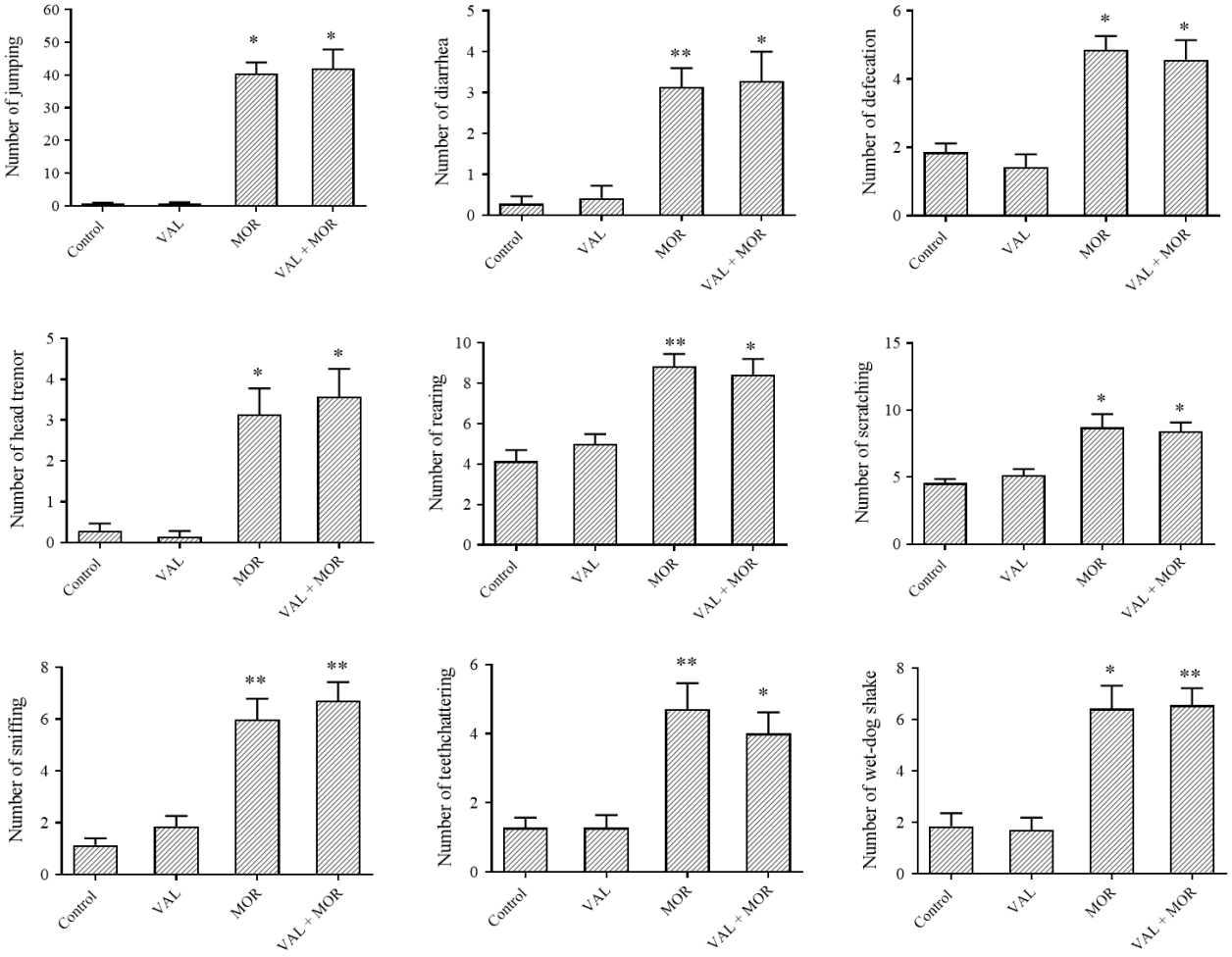

Fig. 4. The effect of acute treatment with VAL on MOR dependence expression. Data are expressed as mean ± SEM (n = 6). **P* < 0.05, **P* < 0.05, and ***P* < 0.01 indicate significant differences compared with the control group. MOR, Morphine; VAL, valsartan.

In order to assess the effect of VAL on the expression of MOR dependence, we administered VAL only once 45 min before the last dose of MOR on the 7th day of the experiment in the animals that had received only MOR. The animals in the control and VAL groups demonstrated no withdrawal signs, whereas the MOR-administered animals exhibited the withdrawal jumps, which confirmed the expression of MOR dependence (Fig. 4). Moreover, acute co-administration of VAL with MOR had no effect on the frequency of withdrawal signs which indicated that VAL could not prevent the expression of MOR dependence.

DISCUSSION

The results of the current study showed that VAL (20 mg/kg, p.o.) had no remarkable effect on the analgesic responses in normal animals. Moreover, we found that VAL significantly protected rats from inducing MOR tolerance and dependence. We also established that VAL had no considerable effect on the expression of MOR tolerance and dependence.

Despite the recent progress in comprehending opioid tolerance and dependence, the exact underlying mechanisms of these phenomena are still poorly understood (23). The induction and expression of tolerance and dependence are the main problems associated with the chronic use of these drugs. Therefore, the identification of compounds that can prevent these processes may have an important use in clinical centers for the management of pain (24). It is well-established that angiotensin II can alter the MOR effects such as withdrawal signs and self-administration (18,19). In these reports, the

level of angiotensin II was reduced by inhibiting the angiotensin-converting enzyme by captopril. Inhibiting the angiotensin-converting enzyme also increased the bradykinin and substance P levels which are potent mediators of pain (25). In another study, it was found that captopril potentiated morphine analgesia, but losartan had no effects on the morphine analgesia response. It is important to mention that in this study, the acute effect of these drugs was evaluated (21). We also found that the acute administration of VAL had no impact on the MOR-analgesia effects and withdrawal signs.

Chronic treatment with MOR can induce apoptosis and neuronal degeneration which leads to structural changes in the brain (24,26). Several investigations have reported MOR-induced neuronal death by increasing the production of free radicals and oxidative stress (27,28). Interestingly, it was reported that reducing the neuronal apoptosis and oxidative status could mitigate the tolerance and dependence induced by MOR (29-31). On the other hand, the neuroprotective effects of VAL were demonstrated in stroke. Wakai *et al*. demonstrated that VAL had neuroprotective effects against transient forebrain ischemia *via* reducing the production of reactive oxygen species as well as the release of cytochrome C (13). VAL potentiates the brain's antioxidant defense system (superoxide dismutase and catalase), decreases the oxidative markers (malondialdehyde), and reduces the neuronal damage in streptozotocin-induced dementia in rats (12). Moreover, the neuroprotection and antioxidant effects of other sartans have been reported. For example, blocking the AT1 receptor with losartan prevented the cognitive deficits and neuropathological lesions in an Alzheimer's disease model *via* mitigating the oxidative stress (14). In another study, candesartan and telmisartan decreased the lesion volume, neuronal injury, and apoptosis in traumatic brain injury (15). Furthermore, losartan enhanced both short-term and long-term memory *via* decreasing the oxidative stress status in the hippocampus (32). Thus, it seems that VAL can reduce the induction of MOR tolerance and dependence *via* antioxidant and neuroprotective properties.

Accumulating evidences indicate that inflammation plays important role in the induction of MOR tolerance and dependence. Chronic MOR administration increases the production of pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) (33,34). Blocking the AT1 receptors in the brain can be used as a treatment for inflammatory brain disorders such as stroke, cerebral hemorrhage, and traumatic brain injury (5). Recent clinical and experimental data show the anti-inflammatory effects of VAL in different conditions. VAL attenuates diabetic nephropathy *via* ameliorating the levels of IL-1β, IL-6, and TNF-α (6). Moreover, VAL has been shown to reduce the levels of IL-6 and TNF-α in patients after interventional therapy for acute myocardial infarction (37) indicating that the effect of VAL might be possibly mediated by an anti-inflammatory mechanism.

NMDA receptor, as a glutamate receptor, is known to play a role in MOR tolerance and dependence *via* increasing the inflow of calcium and trigger inflammatory processes in the brain (23). On the other hand, it has been found that angiotensin II stimulates the release of glutamate (16). Zhou *et al*. demonstrated that blocking the AT1 receptor attenuated the pressor effect through the downregulation of NMDA receptors in the rostral ventrolateral medulla in rats (17). Hence, there is the possibility that VAL could mitigate the induction of MOR tolerance and dependence *via* inhibiting the glutamate release as well as the downregulation of NMDA receptors.

CONCLUSION

Our results indicated that VAL had a remarkable effect on the induction of MOR tolerance and dependence. The results revealed that oral administration of VAL had no effect on the analgesic response. Moreover, acute administration of VAL had no effect on the expression of MOR tolerance and dependence. Since VAL, as an antagonist of AT1 receptor, could attenuate the induction of MOR tolerance and dependence, it seems that these receptors are involved in this phenomenon and further studies are required to clarify the exact underlying mechanisms.

Acknowledgments

This study was financially supported by Rafsanjan University of Medical Sciences under Grant No. 98293.

Conflict of interest statement

The authors declared no conflict of interest in this study.

Authors' contribution

A. Kaeidi and I. Fatemi conceived and designed the experiments. A. Kaeidi, M. Amirteimoury, M.S. Zare, and A. Nazeri performed the experiments. A. Kaeidi and J. Hassanshahi analyzed the data. A. Kaeidi, I. Fatemi, and J. Hassanshahi contributed to providing the reagents, materials, and analysis tools. I. Fatemi and E. Hakimizadeh wrote the paper.

REFERENCES

1. Somogyi AA, Barratt DT, Coller JK. Pharmacogenetics of opioids. Clin Pharmacol Ther. 2007;81(3):429-444. DOI: 10.1038/sj.clpt.6100095.
2. Hemati K, Pourhanifeh MH, Dehdashtian E, Fatemi I, Mehrzadi S, Reiter RJ, *et al*. Melatonin and morphine: potential beneficial effects of co-use. Fundam Clin Pharmacol. 2021;35(1):25-39. DOI: 10.1111/fcp.12566.
3. Rezazadeh H, Hosseini Kahnouei M, Hassanshahi G, Allahtavakoli M, Shamsizadeh A, Roohbakhsh A, *et al*. Regulatory effects of chronic low-dose morphine on nitric oxide level along with baroreflex sensitivity in two-kidney one-clip hypertensive rats. Iran J Kidney Dis. 2014;8(3):194-200.
4. Xin W, Chun W, Ling L, Wei W. Role of melatonin in the prevention of morphine-induced hyperalgesia and spinal glial activation in rats: protein kinase C pathway involved. Int J Neurosci. 2012;122(3):154-163. DOI: 10.3109/00207454.2011.635828.
5. Fatemi I, Amirteimoury M, Shamsizadeh A, Kaeidi A. The effect of metformin on morphine analgesic tolerance and dependence in rats. Res Pharm Sci. 2018;13(4):316-323. DOI: 10.4103/1735-5362.235158.
6. Listos J, Łupina M, Talarek S, Mazur A, Orzelska-Górka J, Kotlińska J. The mechanisms involved in morphine addiction: an overview. Int J Mol Sci. 2019;20(17):4302-4324. DOI: 10.3390/ijms20174302.
7. Cahill CM, Walwyn W, Taylor AMW, Pradhan AAA, Evans CJ. Allostatic mechanisms of opioid tolerance beyond desensitization and downregulation. Trends Pharmacol Sci. 2016;37(11):963-976. DOI: 10.1016/j.tips.2016.08.002.
8. Hassanipour M, Rajai N, Rahimi N, Fatemi I, Jalali M, Akbarian R, *et al*. Sumatriptan effects on morphine-induced antinociceptive tolerance and physical dependence: the role of nitric oxide. Eur J Pharmacol. 2018;835:52-60. DOI: 10.1016/j.ejphar.2018.07.021.
9. Osmanlıoğlu HO, Yıldırım MK, Akyuva Y, Yıldızhan K, Nazıroğlu M. Correction to: morphine induces apoptosis, inflammation, and mitochondrial oxidative stress *via* activation of TRPM2 channel and nitric oxide signaling pathways in the hippocampus. Mol Neurobiol. 2020;57(8):3390. DOI: 10.1007/s12035-020-01992-5.
10. Song L, Wu C, Zuo Y. Melatonin prevents morphine-induced hyperalgesia and tolerance in rats: role of protein kinase C and N-methyl-D-aspartate receptors. BMC Anesthesiol. 2015;15(1):12-20. DOI: 10.1186/1471-2253-15-12.
11. Ismail H, Mitchell R, McFarlane SI, Makaryus AN. Pleiotropic effects of inhibitors of the RAAS in the diabetic population: above and beyond blood pressure lowering. Curr Diab Rep. 2010;10(1):32-36. DOI: 10.1007/s11892-009-0081-y.
12. Abbassi YA, Mohammadi MT, Foroshani MS, Sarshoori JR. Captopril and valsartan may improve cognitive function through potentiation of the brain antioxidant defense system and attenuation of oxidative/nitrosative damage in STZ-induced dementia in rat. Adv Pharm Bull. 2016;6(4):531-539. DOI: 10.15171/apb.2016.067.
13. Wakai T, Yoshioka H, Yagi T, Kato T, Kinouchi H. Effects of valsartan on neuroprotection and neurogenesis after ischemia. Neuroreport. 2011;22(8):385-390. DOI: 10.1097/WNR.0b013e328346be84.
14. Ongali B, Nicolakakis N, Tong XK, Aboulkassim T, Papadopoulos P, Rosa-Neto P, *et al*. Angiotensin II type 1 receptor blocker losartan prevents and rescues cerebrovascular, neuropathological and cognitive deficits in an Alzheimer's disease model. Neurobiol Dis. 2014;68:126-136. DOI: 10.1016/j.nbd.2014.04.018.
15. Villapol S, Balarezo MG, Affram K, Saavedra JM, Symes AJ. Neurorestoration after traumatic brain injury through angiotensin II receptor blockage. Brain. 2015;138(Pt 11):3299-3315. DOI: 10.1093/brain/awv172.
16. Gabor A, Leenen FHH. Cardiovascular effects of angiotensin II and glutamate in the PVN of Dahl salt-sensitive rats. Brain Res. 2012;1447:28-37. DOI: 10.1016/j.brainres.2012.01.060.
17. Zhou X, Yang H, Song X, Wang J, Shen L, Wang J. Central blockade of the AT1 receptor attenuates pressor effects *via* reduction of glutamate release and downregulation of NMDA/AMPA receptors in the rostral ventrolateral medulla of rats with stress-induced hypertension. Hypertens Res. 2019;42(8):1142-1151. DOI: 10.1038/s41440-019-0242-6.
18. Hosseini M, Alaei HA, Headari R, Eslamizadeh MJ. Effects of microinjection of angiotensin II and captopril into nucleus accumbens on morphine self-administration in rats. Indian J Exp Biol. 2009;47(5):361-367.

19. Hosseini M, Sharifi MR, Alaei H, Shafei MN, Karimooy HAN. Effects of angiotensin II and captopril on rewarding propreties of morphine. Indian J Exp Biol. 2007;45(9):770-777.
20. Alaei H, Hosseini M. Angiotensin converting enzyme inhibitor captopril modifies conditioned place preference induced by morphine and morphine withdrawal signs in rats. Pathophysiology. 2007;14(1):55-60.
DOI: 10.1016/j.pathophys.2007.01.002.
21. Hajhashemi V, Zeinvand H. Effects of lisinopril, captopril and losartan alone or in combination with morphine in light tail flick analgesic test. Res Pharm Sci. 2009;2(2):97-101.
22. Yang WN, Hu XD, Han H, Shi LL, Feng GF, Liu Y, *et al*. The effects of valsartan on cognitive deficits induced by aluminum trichloride and d-galactose in mice. Neurol Res. 2014;36(7):651-658.
DOI: 10.1179/1743132813Y.0000000295.
23. Zhao J, Xin X, Xie GX, Palmer PP, Huang YG. Molecular and cellular mechanisms of the age-dependency of opioid analgesia and tolerance. Mol Pain. 2012;8:38-49.
DOI: 10.1186/1744-8069-8-38.
24. Robinson TE, Kolb B. Structural plasticity associated with exposure to drugs of abuse. Neuropharmacology. 2004;47(Suppl 1):33-46.
DOI: 10.1016/j.neuropharm.2004.06.025.
25. Matchar DB, McCrory DC, Orlando LA, Patel MR, Patel UD, Patwardhan MB, *et al*. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. Ann Intern Med. 2008;148(1):16-29.
DOI: 10.7326/0003-4819-148-1-200801010-00189.
26. Atici S, Cinel L, Cinel I, Doruk N, Aktekin M, Akca A, *et al*. Opioid neurotoxicity: comparison of morphine and tramadol in an experimental rat model. Int J Neurosci. 2004;114(8):1001-1011.
DOI: 10.1080/00207450490461314.
27. Ndengele MM, Cuzzocrea S, Masini E, Vinci MC, Esposito E, Muscoli C, *et al*. Spinal ceramide modulates the development of morphine antinociceptive tolerance *via* peroxynitrite-mediated nitroxidative stress and neuroimmune activation. J Pharmacol Exp Ther. 2009;329(1):64-75.
DOI: 10.1124/jpet.108.146290.
28. Salvemini D, Little JW, Doyle T, Neumann WL. Roles of reactive oxygen and nitrogen species in pain. Free Radic Biol Med. 2011;51(5):951-966.
DOI: 10.1016/j.freeradbiomed.2011.01.026.
29. Mori T, Ito S, Matsubayashi K, Sawaguchi T. Comparison of nitric oxide synthase inhibitors, phospholipase A2 inhibitor and free radical scavengers as attenuators of opioid withdrawal syndrome. Behav Pharmacol. 2007;18(8):725-729.
DOI: 10.1097/FBP.0b013e3282f18da6.
30. Ozmen I, Naziroglu M, Alici HA, Sahin F, Cengiz M, Eren I. Spinal morphine administration reduces the fatty acid contents in spinal cord and brain by increasing oxidative stress. Neuroch Res. 2007;32(1):19-25.
DOI: 10.1007/s11064-006-9217-5.
31. Muscoli C, Cuzzocrea S, Ndengele MM, Mollace V, Porreca F, Fabrizi F, *et al*. Therapeutic manipulation of peroxynitrite attenuates the development of opiate-induced antinociceptive tolerance in mice. J Clin Invest. 2007;117(11):3530-3539.
DOI: 10.1172/JCI32420.
32. Bild W, Hritcu L, Stefanescu C, Ciobica A. Inhibition of central angiotensin II enhances memory function and reduces oxidative stress status in rat hippocampus. Prog Neuropsychopharmacol Biol Psychiatry. 2013;43:79-88.
DOI: 10.1016/j.pnpbp.2012.12.009.
33. Saffar S, Fatemi I, Rahmani M, Hassanshahi J, Sahamsizadeh A, Allahtavakoli M, *et al*. The effect of epigallocatechin-3-gallate on morphine-induced memory impairments in rat: EGCG effects on morphine neurotoxicity. Hum Exp Toxicol. 2020;39(7):994-1002.
DOI: 10.1177/0960327120909540.
34. Shibani F, Sahamsizadeh A, Fatemi I, Allahtavakoli M, Hasanshahi J, Rahmani M, *et al*. Effect of oleuropein on morphine-induced hippocampus neurotoxicity and memory impairments in rats. Naunyn Schmiedebergs Arch Pharmacol. 2019;392(11):1383-1391.
DOI: 10.1007/s00210-019-01678-3.
35. Saavedra JM. Angiotensin II AT1 receptor blockers as treatments for inflammatory brain disorders. Clin Sci (Lond). 2012;123(10):567-590.
DOI: 10.1042/CS20120078.
36. Makary S, Abdo M, Hassan WA, Tawfik MK. Angiotensin blockade attenuates diabetic nephropathy in hypogonadal adult male rats. Can J Physiol Pharmacol. 2019;97(8):708-720.
DOI: 10.1139/cjpp-2018-0572.
37. Gong X, Zhou R, Li Q. Effects of captopril and valsartan on ventricular remodeling and inflammatory cytokines after interventional therapy for AMI. Exp Ther Med. 2018;16(4):3579-3583.
DOI: 10.3892/etm.2018.6626.