

Modafinil Improves Catalepsy in a Rat 6-Hydroxydopamine Model of Parkinson's Disease; Possible Involvement of Dopaminergic Neurotransmission

Reza Vajdi-Hokmabad¹, Mojtaba Ziaee², Saeed Sadigh-Eteghad³, Siamak Sandoghchian Shotorbani⁴, Javad Mahmoudi^{3*}

¹ Department of veterinary, Miyaneh branch, Islamic Azad University, Miyaneh, Iran.

² Medicinal Plant Research Center, Institute of Medicinal Plants, ACECR, Karaj, Iran.

³ Neurosciences Research Center (NSRC), Tabriz University of Medical Sciences, Tabriz, Iran.

⁴ Department of Immunology, Tabriz Branch, Islamic Azad University, Tabriz, Iran.

Article info

Article History:

Received: 21 November 2016

Revised: 13 July 2017

Accepted: 16 July 2017

ePublished: 25 September 2017

Keywords:

- 6-hydroxydopamine
- Dopaminergic neurotransmission
- Modafinil
- Parkinson's disease
- Rat

Abstract

Purpose: Modafinil is a vigilance-enhancing drug licensed for narcolepsy. The use of modafinil leads to various neuromodulatory effects with very low abuse potential. A body of evidence suggested that modafinil may have anti-parkinsonian effects. This study was designed to evaluate whether modafinil could improve motor dysfunction in the 6-hydroxydopamine (6-OHDA)-induced rat model of Parkinson's disease.

Methods: Male Wistar rats (180-220 g, n= 98) were used in this study. Parkinsonism was induced by injection of 6-hydroxydopamine (10 µg/2µl in 0.2 % ascorbic acid-saline) into the right striatum. Parkinsonian rats received intraperitoneal (ip) injections of modafinil (50, 75, and 100 mg/kg) and catalepsy-like immobility was assessed by the bar test (BT). Furthermore, involvement of dopamine D₁ and D₂ receptors in modafinil's anti-parkinsonian effects was studied. For this purpose, parkinsonian animals were pretreated with SCH23390 and raclopride (the dopamine D₁ and D₂ receptor antagonists, respectively) or SCH23390 + raclopride, and then assessed by the BT.

Results: Modafinil (100 mg/kg) showed anti-cataleptic effects in the BT. Notably, the effect of modafinil in the BT was reversed in parkinsonian rats pretreated with raclopride (1.25 mg/kg) and/or SCH23390 + raclopride (0.75 and 1.25 mg/kg, respectively), but not in those pretreated with SCH23390 (0.75 mg/kg).

Conclusion: Acute administration of modafinil improves 6-OHDA-induced motor impairment possibly through activation of dopamine D₂ receptors.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative condition characterizing with motor symptoms including akinesia, bradykinesia, tremor at rest, rigidity¹ and leads to extensive biochemical and molecular alterations in cerebral structures that are involved in motor function.^{2,3} Dopamine (DA) regulates normal motor activity through D₁ and D₂ receptors that are found postsynaptically on the dopaminergic (DAergic) neurons⁴ in the striatum.⁵ Studies showed that degeneration of the nigrostriatal pathway alters the brain's D₁ and D₂ receptor densities.^{6,7} Such changes play a compensatory role and may consider as a promising therapeutic target in PD.⁸

L-DOPA (3,4-dihydroxyphenylalanine) restores DA level to normal value, but responses to this regimen decline over the time and the patients experience some motor abnormalities.⁹ Hence, development of effective therapies to manage PD complications is of great interest.

Modafinil is a vigilance-enhancing compound¹⁰ first approved by the Food and Drug Administration for treatment of sleep disorders such as narcolepsy, shift-work sleep disorder and obstructive-sleep apnea syndrome.^{11,12} Because of its complex and wide spectrum pharmacologic profiles, there are efforts for its application in conditions such as nicotine and cocaine addiction,¹¹ schizophrenia, memory impairments, depression¹³ and PD.^{10,14} Results of positron-emission tomography (PET)¹⁵ and microdialysis¹⁶ studies have shown that modafinil has the ability to increase cerebral DA levels. Given the above, modafinil appears to provide anti-PD effects via modulation of DAergic neurotransmission. Therefore, the present study was set out to evaluate modafinil's anti-parkinsonian effects in a rat model of PD and the involvement of D₁ and D₂ DAergic receptors in this effect.

*Corresponding author: Javad Mahmoudi, Tel/Fax: +98-41-33340730, Email: mahmoudij@tbzmed.ac.ir

©2017 The Authors. This is an Open Access article distributed under the terms of the Creative Commons Attribution (CC BY), which permits unrestricted use, distribution, and reproduction in any medium, as long as the original authors and source are cited. No permission is required from the authors or the publishers.

Materials and Methods

Animals

Ninety eight male Wistar rats weighing 180-220 g were used for the experiment. Animals were kept under controlled conditions (12/12 h light /dark cycle: lights on at 07: 00 hours, ambient temperature $21\pm 1^\circ\text{C}$, humidity $55\pm 5\%$) with unrestricted access to food and water.

Drugs and treatments

All chemicals were purchased from Sigma-Aldrich Chemical Co. (USA). For systemic administration, modafinil was suspended in saline with 0.4% sodium carboxymethyl cellulose. SCH23390 (the DA D_1 receptor antagonist) and raclopride (the DA D_2 receptor antagonist) were dissolved in distilled water. 6-OHDA was dissolved in a 0.9% normal saline solution containing 0.2% (w/v) ascorbic acid. Drugs were freshly prepared and injected intraperitoneally (ip) in a volume of 1 ml/kg body weight, except for 6-OHDA which was injected into the right striatum. Desipramine (25 mg/kg, ip) was injected 30 min before intra-striatal injection of 6-OHDA, in order to prevent the destruction of noradrenergic neurons.¹⁷

Two sets of experiments were performed in this study. The first experiment was conducted to assess modafinil's ability to reduce the immobility time in parkinsonian animals. In this phase, rats with 6-OHDA lesion received different doses of modafinil (50, 75, and 100 mg/kg) or its vehicle and then, after 30 minutes, were subjected to the bar test (BT).

The second set was carried out to evaluate the possible involvement of the DAergic system on the anti-immobility effect of modafinil in the BT. In this phase, individual groups of parkinsonian animals were pretreated with SCH23390 (0.75 mg/kg, ip), raclopride (1.25 mg/kg, ip) and/or both of these (or their vehicles) at the same doses in combination, and after 30 minutes, received modafinil (100 mg/kg) or the its vehicle. The doses of antagonists used in this study was approximately the same as that reported by Hauber *et al.*¹⁸

Intra-striatal injection of 6-OHDA

For stereotaxic surgery, animals were anesthetized with a combination of ketamine and xylazine (80 and 5 mg/kg, ip; respectively) and placed in a stoelting stereotaxic apparatus (stoelting, USA) in the flat skull position. The small central incision was made to make the skull appear. A 23 gauge sterile cannula was inserted into the injection site as a guide cannula for subsequent insertion of the injection tube into the striatum. The coordinates for this position, with reference to the atlas of Paxinos & Watson,¹⁹ were: anteroposterior from bregma (AP)= 0.4 mm, mediolateral from the midline (ML)= 2.8 mm and dorsoventral from the skull (DV)= -5 mm. Subsequently, 6-OHDA (10 μg / rat in 2 μl saline containing 0.2% ascorbic acid) was infused by an infusion pump at the flow rate of 0.2 $\mu\text{l}/\text{min}$ into the right striatum. Lesioned rats were subjected to the designed

protocols after a 3-week recovery period. All of these procedures were performed for sham-operated animals, but they only received intra-striatal of 2 μl vehicle of 6-OHDA (0.9% saline containing 0.2% (w/v) ascorbic acid).

Assessment of catalepsy-like immobility

Catalepsy-like immobility was assessed by using BT. As described previously, both forelegs of a rat were gently placed over a 9-cm-high horizontal bar (diameter, 0.7 cm) and the retention time in this imposed posture was considered to define catalepsy time. The end point of catalepsy was designated to occur when both front paws were removed from the bar or the animal moved its head in an exploratory fashion. The cut-off time of the test was 180 seconds.^{17,20}

Verification of infusion site

To verify the infusion site, all rats were sacrificed by a high dose of ether at the end of behavioral assessments. Afterwards, the brains were removed and stored in 10% formaldehyde solution for one week prior to embedding and sectioning. Serial coronal sections (6 μm) were taken with a microtome (Leitz, Germany) and stained with haematoxylin-eosin; the scar tract made by the infusion tube was controlled with a light microscope. Whenever the emplacement of the infusion tube in striatum was incorrect, the representative data were excluded.

Statistical analysis

Statistical analysis of each data set was done by SPSS 21 software. The data were expressed as the mean \pm SEM and were analyzed by two-and/or one-way ANOVA and post hoc Tukey's test. *P* values < 0.05 were considered to be statistically significant.

Results

Effect of 6-OHDA on the BT

One-way ANOVA revealed a significant effect of intra-striatal injection of 6-OHDA [$F(3,28)=375.27$ $p<0.001$] on the catalepsy time in comparison with control and sham-operated groups. Post hoc analysis showed that 6-OHDA (10 μg / rat) increased catalepsy time in the BT, which indicates that this neurotoxin is able to produce marked catalepsy. Also, there was no significant difference between the sham-operated group and control rats (Figure 1).

Effect of modafinil on the BT

One-way ANOVA showed that modafinil could attenuate catalepsy time in 6-OHDA-lesioned rats [$F(3,28) = 375.27$ $p<0.001$]. Post hoc analysis indicated that modafinil only at the dose of 100 mg/kg is able to decrease the immobility time in the BT when compared with vehicle-treated 6-OHDA-lesioned rats. At lower doses (50 and 75 mg/kg), modafinil has not significant effect on the catalepsy time (Figure 1).

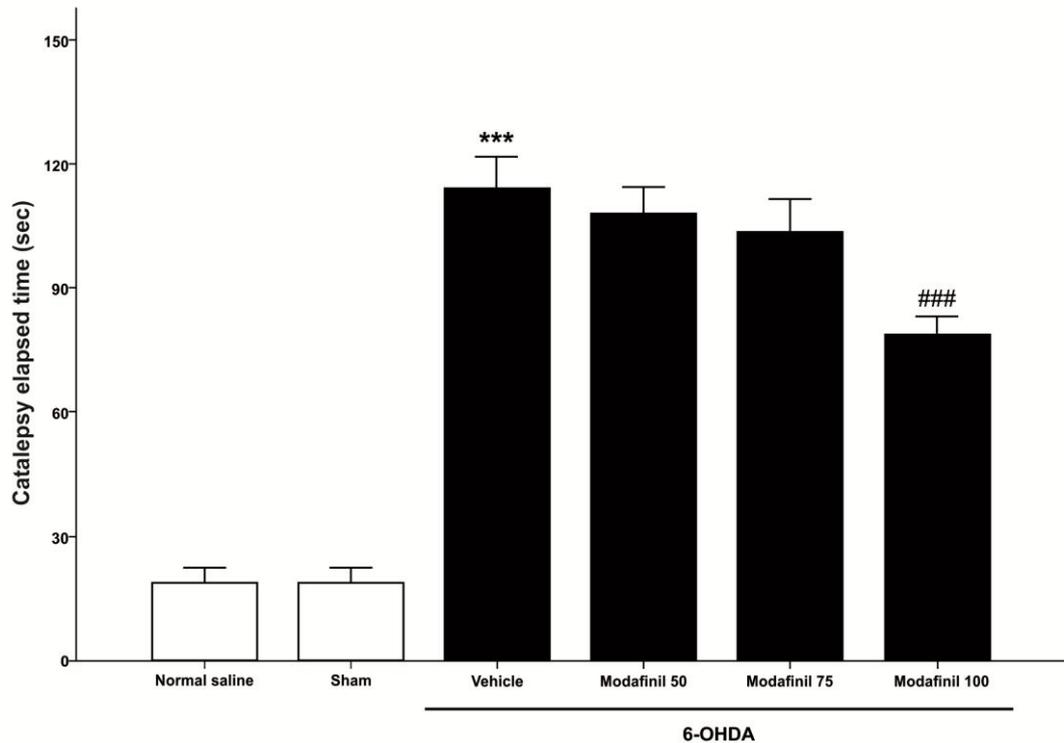


Figure 1. Effect of intraperitoneal (ip) injection of vehicle and/or different doses of modafinil (50, 75 and 100 mg/kg) on the 6-OHDA (10 µg/2 µl/rat)-induced catalepsy. Each bar represents the mean ± SEM. (n = 8) *** $p < 0.001$ and ### $p < 0.001$ as compared with the normal saline and vehicle received groups, respectively.

Effect of raclopride and SCH23390 pretreatment on the anti-cataleptic effect of modafinil

Modafinil (100 mg/kg, ip) reduced catalepsy ($p < 0.001$) and the involvement of the DAergic neurotransmission on this effect was studied in separate groups of 6-OHDA-lesioned rats.

A two-way ANOVA revealed significant differences of modafinil treatment [$F(1,28) = 55.3$ $p < 0.001$] but not SCH23390 pretreatment [$F(1,28) = 0.8$ $p > 0.05$]. Also, there was significant differences of modafinil treatment interaction with SCH23390 pretreatment [$F(1,28) = 18$ $p < 0.001$].

The results presented in in Figure 2A, show that pretreatment of lesioned rats with SCH23390 (0.75 mg/kg, ip) did not alter the anti-cataleptic effect of modafinil in the BT.

A two-way ANOVA showed significant differences of modafinil treatment [$F(1, 28) = 143.7$ $p < 0.001$], raclopride pretreatment [$F(1, 28) = 91.2$ $p < 0.001$] and modafinil treatment interaction with raclopride pretreatment [$F(1, 28) = 6.92$ $p < 0.05$].

The results presented in Figure 2B show that pretreatment of lesioned rats with raclopride (1.25 mg/kg, ip) reversed the anti-cataleptic effect of modafinil in the BT.

A two-ANOVA revealed significant differences of modafinil treatment [$F(1, 28) = 169.8$ $p < 0.001$], SCH23390 + raclopride pretreatment [$F(1, 28) = 218.9$ $p < 0.001$] and modafinil treatment interaction with SCH23390 + raclopride pretreatment [$F(1, 28) = 8.94$ $p < 0.01$]. The results depicted in Figure 2C show that

pretreatment of lesioned rats with SCH23390 + raclopride (0.75 and 1.25 mg/kg, respectively, ip) blocked anti-cataleptic effect of modafinil in the BT.

Discussion

Our data showed that modafinil displays an anti-parkinsonian effect on the 6-OHDA lesioned rats, and this effect in part is mediated through DAergic neurotransmission.

Catalepsy or tonic immobility is a complex motor inhibition²¹ in which rodents are unable to correct externally imposed abnormal posture^{21,22} and revert to a normal position for initiation of exploratory behavior.²³ This behavior not only is able to mimic the state of akinesia and rigidity occurring in PD²⁴ but also is used to evaluate nigrostriatal function and its regulation by different neurotransmitter systems.²⁵ 6-OHDA is frequently used for chemical denervation of DAergic neurons²⁶ and those rats with DAergic lesion show marked catalepsy;²⁷ as a result, this neurotoxin provides simple and a reliable model for studying the anti-parkinsonian potential of drugs.²⁰

In this study, a single dose of modafinil (100 mg/kg) resulted in decreased catalepsy time and normalized motor behavior in parkinsonian rats 30 min after ip injection. Pharmacokinetic findings suggest that modafinil reaches a peak concentration in brain 30 to 60 min by single systemic administration²⁸ and produces a rapid and significant elevation in brain DA content in dose dependent fashion.²⁹

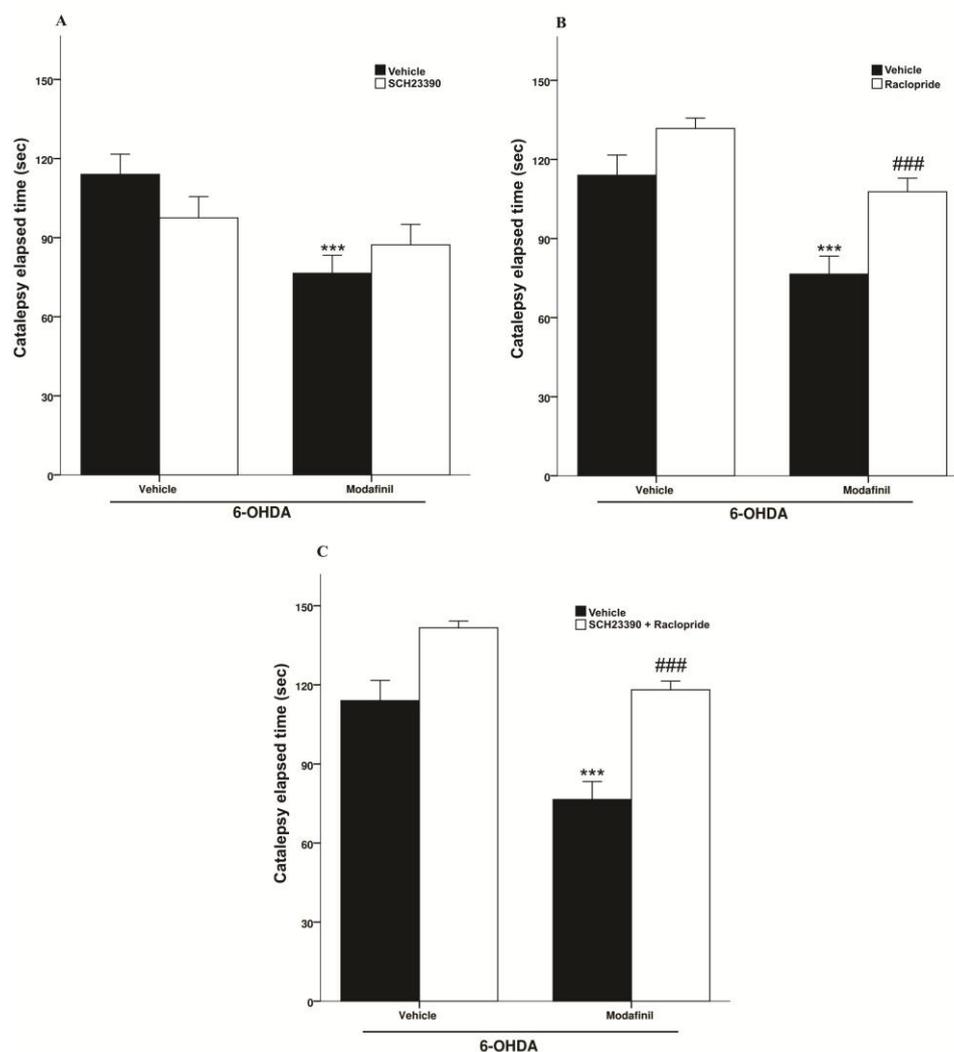


Figure 2. Effect of pretreatment with SCH23390 (0.75 mg/kg) (A), raclopride (1.25 mg/kg) (B) and/or SCH23390 + raclopride (0.75 + 1.25 mg/kg, respectively) (C) on the modafinil anti-cataleptic effect. Each bar represents the mean \pm SEM. (n = 8) *** p <0.001 and ### p <0.01 as compared with the vehicle and the modafinil (100 mg/kg, ip) injected rats, respectively.

Nucleus accumbens which receives DAergic inputs from the ventral tegmental area and medial substantia nigra regulates normal motor function.^{30,31} Modafinil increases DA efflux in this region³² through inhibition of DA transports¹⁶ as well as reduction of accumbal GABAergic tone. The inhibitory effect of modafinil on the GABAergic system also enhances the activity of the striatopallidal pathway.³³ This pathway governs normal motor function and is involved in the appearance of PD motor signs.³⁴

In another portion of this study, parkinsonian rats pretreated with concomitant administration of D₁ and D₂ receptor antagonists (raclopride and SCH23390, respectively). This intervention increased immobility time in the BT and prevented the anti-parkinsonian effects of modafinil. Furthermore, blockade of D₂ receptors using raclopride reversed the anti-parkinsonian effect of modafinil in 6-OHDA lesioned rats.

Studies on the striatal D₂ receptor suggested that denervation of DAergic neurons by 6-OHDA might increase D₂ receptor densities from 2-8 weeks post-lesion

in impacted animals.³⁵ Indeed, significant up-regulation of post synaptic D₂ receptor binding sites is accompanied by elevation of D₂ mRNA levels in 6-OHDA lesioned rats.^{36,37} Moreover, postmortem studies in drug-naïve PD patients have also confirmed such increase in striatal D₂ receptor binding sites.³⁸

Contrary to D₂ receptors, there is contradictory evidence about D₁ receptor alterations in parkinsonian rats.³⁵⁻³⁹

While there are no reports showing that alteration in D₁ density happens in PD,³⁸ Zhao et al. showed that a decline in mRNA levels for D₁ receptors in DA-lesioned striatum occurs in parkinsonian rats.⁷ This reflects that denervation of DAergic structures is not able to increase D₁ receptors densities.³⁵

Decline in striatal DA levels causes an imbalance in striatal functions and disrupts normal motor activity. Hence, pronounced up-regulation of D₂ receptors may potentiate responsiveness to decreased levels of striatal DA and normalize motor activity,⁸ especially in *de novo* and young parkinsonian patients.⁴⁰ Moreover, when compared with D₂ receptors, D₁ receptors have less

ability to increase locomotor activity.⁴¹ Collectively, these data can explain why D₂ receptor activation may in part mediate anti-parkinsonian effects of modafinil.

Complications such as development of abnormal motor fluctuation and inadequate responses to standard anti-parkinsonian drugs remain major problems in parkinsonian patients.^{20,42} In addition, non-motor comorbidities such as depression⁴³ and sleep disorders^{44,45} are experienced by the majority of patients and impact their daily living activities.

Hence, application of regimens to overcome these problems is of great importance; the ability of modafinil to reduce PD symptoms in experimental models, as well as its potential for anti-depressant-like properties in preclinical research and treatment of sleep disorders in PD, suggests that modafinil may have potential to improve the effectiveness of current anti-PD medications.

Conclusion

In conclusion, this study showed that modafinil improves catalepsy behavior in a rat model of PD. Considering the role of DAergic neurotransmission in regulation of normal motor behavior and alterations of D₂ receptor densities in PD, it may be suggested that modafinil exert the anti-PD effect through modulation of DAergic system. Moreover, the complexity of modafinil's mechanism of action suggests that more experiments must be designed to reveal its neuropharmacological effects.

Acknowledgments

We would like to express our special gratitude to the Miyaneh branch of Islamic Azad University, Iran, for financial support.

Ethical Issues

The experiment was performed in accordance with the Guide and Use of Laboratory Animals (National Institutes of Health) and confirmed by the Ethical Committee for Animal Experimentation of the Miyaneh branch of Islamic Azad University.

Conflict of Interest

The authors declare no conflict of interests.

References

- Haddadi R, Mohajjel Nayebi A, Brooshghalan SE. Pre-treatment with silymarin reduces brain myeloperoxidase activity and inflammatory cytokines in 6-ohda hemi-parkinsonian rats. *Neurosci Lett* 2013;555:106-11. doi: 10.1016/j.neulet.2013.09.022
- Nagatsu T, Sawada M. Biochemistry of postmortem brains in Parkinson's disease: historical overview and future prospects. *J Neural Transm Suppl* 2007(72):113-20.
- Shih MC, Hoexter MQ, Andrade LA, Bressan RA. Parkinson's disease and dopamine transporter neuroimaging: A critical review. *Sao Paulo Med J* 2006;124(3):168-75.
- Beaulieu JM, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol Rev* 2011;63(1):182-217. doi: 10.1124/pr.110.002642
- Paul ML, Graybiel AM, David JC, Robertson HA. D1-like and D2-like dopamine receptors synergistically activate rotation and c-fos expression in the dopamine-depleted striatum in a rat model of parkinson's disease. *J Neurosci* 1992;12(10):3729-42.
- Schwartz RK, Huston JP. The unilateral 6-hydroxydopamine lesion model in behavioral brain research. Analysis of functional deficits, recovery and treatments. *Prog Neurobiol* 1996;50(2-3):275-331. doi: 10.1016/s0301-0082(96)00040-8
- Zhao R, Lu W, Fang X, Guo L, Yang Z, Ye N, et al. (6aR)-11-amino-N-propyl-noraporphine, a new dopamine D2 and serotonin 5-HT1A dual agonist, elicits potent antiparkinsonian action and attenuates levodopa-induced dyskinesia in a 6-OHDA-lesioned rat model of Parkinson's disease. *Pharmacol Biochem Behav* 2014;124:204-10. doi: 10.1016/j.pbb.2014.06.011
- Ballion B, Frenois F, Zold CL, Chetrit J, Murer MG, Gonon F. D2 receptor stimulation, but not d1, restores striatal equilibrium in a rat model of parkinsonism. *Neurobiol Dis* 2009;35(3):376-84. doi: 10.1016/j.nbd.2009.05.019
- Mahmoudi J, Farhoudi M, Reyhani-Rad S, Sadigh-Eteghad S. Dampening of serotonergic system through 5HT1A receptors is a promising target for treatment of levodopa induced motor problems. *Adv Pharm Bull* 2013;3(2):439-41. doi: 10.5681/apb.2013.071
- Xiao YL, Fu JM, Dong Z, Yang JQ, Zeng FX, Zhu LX, et al. Neuroprotective mechanism of modafinil on Parkinson disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Acta Pharmacol Sin* 2004;25(3):301-5.
- Dopheide MM, Morgan RE, Rodvelt KR, Schachtman TR, Miller DK. Modafinil evokes striatal [(3)H]dopamine release and alters the subjective properties of stimulants. *Eur J Pharmacol* 2007;568(1-3):112-23. doi: 10.1016/j.ejphar.2007.03.044
- Qu WM, Huang ZL, Xu XH, Matsumoto N, Urade Y. Dopaminergic D1 and D2 receptors are essential for the arousal effect of modafinil. *J Neurosci* 2008;28(34):8462-9. doi: 10.1523/JNEUROSCI.1819-08.2008
- Mahmoudi J, Farhoudi M, Talebi M, Sabermarouf B, Sadigh-Eteghad S. Antidepressant-like effect of modafinil in mice: Evidence for the involvement of the dopaminergic neurotransmission. *Pharmacol Rep* 2015;67(3):478-84. doi: 10.1016/j.pharep.2014.11.005
- Van Vlieta SA, Blezer EL, Jongasma MJ, Vanwersch RA, Olivier B, Philippens IH. Exploring the

- neuroprotective effects of modafinil in a marmoset parkinson model with immunohistochemistry, magnetic resonance imaging and spectroscopy. *Brain Res* 2008;1189:219-28. doi: 10.1016/j.brainres.2007.10.059
15. Madras BK, Xie Z, Lin Z, Jassen A, Panas H, Lynch L, et al. Modafinil occupies dopamine and norepinephrine transporters in vivo and modulates the transporters and trace amine activity in vitro. *J Pharmacol Exp Ther* 2006;319(2):561-9. doi: 10.1124/jpet.106.106583
 16. Zolkowska D, Jain R, Rothman RB, Partilla JS, Roth BL, Setola V, et al. Evidence for the involvement of dopamine transporters in behavioral stimulant effects of modafinil. *J Pharmacol Exp Ther* 2009;329(2):738-46. doi: 10.1124/jpet.108.146142
 17. Reyhani-Rad S, Mohajjel Nayebi A, Mahmoudi J, Samini M, Babapour V. Role of 5-Hydroxytryptamine 1A Receptors in 6-Hydroxydopamine-induced Catalepsy-like Immobilization in Rats: a Therapeutic Approach for Treating Catalepsy of Parkinson's Disease. *Iran J Pharm Res* 2012;11(4):1175-81.
 18. Hauber W, Neuscheler P, Nagel J, Muller CE. Catalepsy induced by a blockade of dopamine D1 or D2 receptors was reversed by a concomitant blockade of adenosine A(2A) receptors in the caudate-putamen of rats. *Eur J Neurosci* 2001;14(8):1287-93. doi: 10.1046/j.0953-816x.2001.01759.x
 19. Paxinos GW, Charles W. The rat brain in stereotaxic coordinates. 5th ed. Burlington, MA: Elsevier Academic Press; 2005.
 20. Mahmoudi J, Mohajjel Nayebi A, Samini M, Reyhani-Rad S, Babapour V. Buspirone improves the anti-cataleptic effect of levodopa in 6-hydroxydopamine-lesioned rats. *Pharmacol Rep* 2011;63(4):908-14. doi: 10.1016/s1734-1140(11)70606-5
 21. Bazhenova EY, Kulikov AV, Tikhonova MA, Bazovkina DV, Fursenko DV, Popova NK. On the association between lipopolysaccharide induced catalepsy and serotonin metabolism in the brain of mice genetically different in the predisposition to catalepsy. *Pharmacol Biochem Behav* 2013;111:71-5. doi: 10.1016/j.pbb.2013.08.009
 22. Fink-Jensen A, Schmidt LS, Dencker D, Schülein C, Wess J, Wörtwein G, et al. Antipsychotic-induced catalepsy is attenuated in mice lacking the M4 muscarinic acetylcholine receptor. *Eur J Pharmacol* 2011;656(1-3):39-44.
 23. Tostes JG, Medeiros P, Melo-Thomas L. Modulation of haloperidol-induced catalepsy in rats by GABAergic neural substrate in the inferior colliculus. *Neuroscience* 2013;255:212-8. doi: 10.1016/j.neuroscience.2013.09.064
 24. Di Matteo V, Pierucci M, Esposito E, Crescimanno G, Benigno A, Di Giovanni G. Serotonin modulation of the basal ganglia circuitry: Therapeutic implication for parkinson's disease and other motor disorders. *Prog Brain Res* 2008;172:423-63. doi: 10.1016/s0079-6123(08)00921-7
 25. Mohajjel Nayebi A, Sheidaei H. Buspirone improves haloperidol-induced parkinson disease in mice through 5-HT(1A) recaptors. *Daru* 2010;18(1):41-5.
 26. Schober A. Classic toxin-induced animal models of parkinson's disease: 6-OHDA and MPTP. *Cell Tissue Res* 2004;318(1):215-24. doi: 10.1007/s00441-004-0938-y
 27. Nayebi AM, Rad SR, Saberian M, Azimzadeh S, Samini M. Buspirone improves 6-hydroxydopamine-induced catalepsy through stimulation of nigral 5-HT(1A) receptors in rats. *Pharmacol Rep* 2010;62(2):258-64.
 28. de Saint Hilaire Z, Orosco M, Rouch C, Blanc G, Nicolaidis S. Variations in extracellular monoamines in the prefrontal cortex and medial hypothalamus after modafinil administration: A microdialysis study in rats. *Neuroreport* 2001;12(16):3533-7.
 29. Ferraro L, Tanganelli S, O'Connor WT, Antonelli T, Rambert F, Fuxe K. The vigilance promoting drug modafinil increases dopamine release in the rat nucleus accumbens via the involvement of a local GABAergic mechanism. *Eur J Pharmacol* 1996;306(1-3):33-9. doi: 10.1016/0014-2999(96)00182-3
 30. Swanson CJ, Kalivas PW. Regulation of locomotor activity by metabotropic glutamate receptors in the nucleus accumbens and ventral tegmental area. *J Pharmacol Exp Ther* 2000;292(1):406-14.
 31. Kalivas PW, Alesdatter JE. Involvement of n-methyl-d-aspartate receptor stimulation in the ventral tegmental area and amygdala in behavioral sensitization to cocaine. *J Pharmacol Exp Ther* 1993;267(1):486-95.
 32. Minzenberg MJ, Carter CS. Modafinil: A review of neurochemical actions and effects on cognition. *Neuropsychopharmacology* 2008;33(7):1477-502. doi: 10.1038/sj.npp.1301534
 33. Ferraro L, Antonelli T, O'Connor WT, Tanganelli S, Rambert FA, Fuxe K. The effects of modafinil on striatal, pallidal and nigral GABA and glutamate release in the conscious rat: Evidence for a preferential inhibition of striato-pallidal GABA transmission. *Neurosci Lett* 1998;253(2):135-8. doi: 10.1016/s0304-3940(98)00629-6
 34. Augustin SM, Beeler JA, McGehee DS, Zhuang X. Cyclic AMP and afferent activity govern bidirectional synaptic plasticity in striatopallidal neurons. *J Neurosci* 2014;34(19):6692-9. doi: 10.1523/JNEUROSCI.3906-13.2014
 35. Araki T, Tanji H, Kato H, Itoyama Y. Sequential changes of dopaminergic receptors in the rat brain after 6-hydroxydopamine lesions of the medial forebrain bundle. *J Neurol Sci* 1998;160(2):121-7. doi: 10.1016/s0022-510x(98)00248-2
 36. Narang N, Wamsley JK. Time dependent changes in da uptake sites, D1 and D2 receptor binding and mrna after 6-ohda lesions of the medial forebrain bundle in

- the rat brain. *J Chem Neuroanat* 1995;9(1):41-53. doi: 10.1016/0891-0618(95)00064-e
37. Przedborski S, Levivier M, Jiang H, Ferreira M, Jackson-Lewis V, Donaldson D, et al. Dose-dependent lesions of the dopaminergic nigrostriatal pathway induced by intrastriatal injection of 6-hydroxydopamine. *Neuroscience* 1995;67(3):631-47. doi: 10.1016/0306-4522(95)00066-r
38. Bezard E, Brotchie JM, Gross CE. Pathophysiology of levodopa-induced dyskinesia: Potential for new therapies. *Nat Rev Neurosci* 2001;2(8):577-88. doi: 10.1038/35086062
39. Blunt SB, Jenner P, Marsden CD. Autoradiographic study of striatal D1 and D2 dopamine receptors in 6-OHDA-lesioned rats receiving foetal ventral mesencephalic grafts and chronic treatment with L-DOPA and carbidopa. *Brain Res* 1992;582(2):299-311. doi: 10.1016/0006-8993(92)90147-2
40. Hisahara S, Shimohama S. Dopamine receptors and Parkinson's disease. *Int J Med Chem* 2011;2011:403039. doi: 10.1155/2011/403039
41. Beninger RJ, Mazurski EJ, Hoffman DC. Receptor subtype-specific dopaminergic agents and unconditioned behavior. *Pol J Pharmacol Pharm* 1991;43(6):507-28.
42. Mahmoudi J, Mohajjel Nayebi A, Reyhani-Rad S, Samini M. Fluoxetine improves the effect of levodopa on 6-hydroxy dopamine-induced motor impairments in rats. *Adv Pharm Bull* 2012;2(2):149-55. doi: 10.5681/apb.2012.023
43. Lemke MR. Dopamine agonists in the treatment of non-motor symptoms of parkinson's disease: Depression. *Eur J Neurol* 2008;15 Suppl 2:9-14. doi: 10.1111/j.1468-1331.2008.02213.x
44. Kumar S, Bhatia M, Behari M. Sleep disorders in Parkinson's disease. *Mov Disord* 2002;17(4):775-81. doi: 10.1002/mds.10167
45. Happe S, Pirker W, Sauter C, Klosch G, Zeitlhofer J. Successful treatment of excessive daytime sleepiness in parkinson's disease with modafinil. *J Neurol* 2001;248(7):632-4. doi: 10.1007/s004150170148