Archives of Advances
in Biosciences

Original Article:

Lysosomal and Dopaminergic D2 Inhibition Reversed the Effect of Morphine on Learning and Memory in Male Wistar Rats Relating Mitochondrial Biogenesis

Solmaz Khalifeh[1*], Mohammad Nasehi[2], Mohammad-Reza Zarrindast[2,3]

1. Department of physiology, Faculty of medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.
2. Cognitive and Neuroscience Research Center (CNRC), Amir-Almomenin Hospital, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.
3. Iranian National Center for Addiction Studies, Tehran University of Medical Sciences, Tehran, Iran.

Cite this article as: Khalifeh S, Nasehi M, Zarrindast MR.. Lysosomal and Dopaminergic D2 Inhibition Reversed the Effect of Morphine on Learning and Memory in Male Wistar Rats Relating Mitochondrial Biogenesis. Archives of Advances in Biosciences. 2023; 14:E39090. https://doi.org/10.22037/aab.v14i. 39090

https://journals.sbmu.ac.ir/aab/article/view/39090

Article info:
Received: 17 May 2023
Accepted: 28 Jan 2023
Published: 20 Jul 2023

*** Corresponding author:**

Solmaz Khalifeh, PhD.

Address Department of physiology, Faculty of medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.

E-mail: -
Soolmaz25kh@yahoo.com

Abstract

Introduction: Opiates dependence has many side effects on body especially brain neuroplasticity leading to changes in behavior. In this study, we evaluated the effects of morphine dependence on learning and memory as well as on Peroxisome proliferator-activated receptor gamma coactivator -1 alpha (PGC-1α) protein level as a key regulator of mitochondrial biogenesis. Also, by using Chloroquine (lysosomal inhibitor) and dopaminergic system inhibitor (Sulpiride), the molecular mechanism, underling morphine addiction related to lysosome, dopamine receptors and mitochondria, has been considered in this study.

Materials and Methods: Male albino Wiastar rats received morphine in their water for 21 days; during the ending 4 days, they received daily intracerebroventricular (i.c.v.) injection of Chloroquine diphosphate (50 mM). Also, i.c.v. injection of Sulpiride (0.25μg/rat) was done before behavioral test. Shuttle box apparatus was used for learning and memory evaluation. After behavioral test, the brains of rats were extracted and the level of PGC-1α protein was investigated by western blotting.

Results: Results indicated that morphine oral administration has reduced learning and memory-like behavior. Pre-training i.c.v. injection of Chloroquine and Sulpiride improved learning and memory. PGC-1α protein level in rats which received Chloroquine and also in the morphine group increased and there was a more significant increase in rats which received morphine, Chloroquine and Sulpiride altogether.

Conclusion: Morphine has an adverse effect on learning and memory as it has been shown with spending more time in dark rooms of Shuttle box apparatus, which was reversed by Chloroquine (lysosomal inhibitor) and dopamine inhibitor (Sulpiride). Increasing PGC-1α protein level may imply the important role of mitochondrial biogenesis in morphine-dependent learning changes. Overall, data suggest dopaminergic system along with lysosome and mitochondrial activity play an important role in morphine addiction status.

Keywords: Learning, Memory, Morphine, Chloroquine, Rat, PGC-1α, Sulpiride

1. Introduction

Addiction is a complex and serious social, economic, and health phenomenon. It is a disorder related to the reward system of the brain, which is caused by transcriptional and epigenetic mechanisms and develops over time by chronically high use of an addictive stimulus (e.g., food, drugs, sexual activities, gambling, etc.)[1, 2]. One of the most commonly used groups is opiates. Morphine is a commonly used opiate that is widely used for patients with acute pain [3]. The efficacy and safety of using opioids as a treatment for chronic pain has not been yet proved to be certain [4]. It has been shown that opioid addiction causes changes in mood and increases anxiety, depression, and cognitive disorders [5, 6]. Furthermore, it causes learning and memory problems [7]. Withdrawal syndrome and dependence occur as a result of long-term use of opioids, such as morphine [8, 9]. Continuous injections of addictive drugs result in neural adaptation and changes in the number and efficiency of opioid receptors, signalling pathways, gene expression, and subsequent protein components [10-14].

Dopamine (DA) is a neurotransmitter which is involved in many neuropsychiatric disorders and has wide effects on many types of cognitive tasks. There are two known family of DA receptors: D1-like receptors that are expressed throughout the brain and include D1 and D5 subtypes, and D2-like receptors that exhibit more regional specificity and include D2, D3 and D4 subtypes. These variations have important consequences for cognition and behaviour. All receptors of DA are slow metabotropic receptors that are related to G proteins. The activation of D1 receptors increases intracellular cAMP levels, whereas the D2 receptors end up with decreasing intracellular cAMP levels. There is some evidence showing that DA has two special effects on neuromodulators: a fast effect which has impacts on postsynaptic glutamate response, and a slow effect that potentiates synaptic plasticity [15]. Additionally, studies have shown the coupling of ERK pathway with D2 receptors activation in the different parts of brain [16-18]. Some studies have shown the role of ERK pathway in dopaminergic neurons, for example in the development of dopaminergic mesencephalic neurons [19, 20]. It has been shown that sulpiride as a dopamine D2 antagonist is practical in working memory [21], and depression symptoms [22].

Chloroquine has been used to treat malaria before. Chloroquine increases the inducement of vacuolization in the cell by increasing lysosomal pH; also, it is used to treat tumors.

In the present research, we studied the intrinsic relation among mitochondria, lysosome and dopaminergic system in morphine addiction by using Chloroquine as autophagy inhibitor and sulpiride (dopamine D2 antagonist) on learning and memory. Moreover, we examined mitochondrial biogenesis by evaluating Peroxisome proliferator-activated receptor gamma coactivator -1 alpha (PGC-1α) protein level in rats with morphine addiction.

2. Materials and Methods

Animals and experimental groups design

Adult male albino rats of Wistar strain (Pasteur Institute, Tehran, Iran) weighing 200-230 gr at the time of surgery were obtained. Each group included eight rats (n=8) and the animals were kept in plastic cage (four/cage) under retention 12-h light/dark cycle (lights on 7:00 a.m.) and persistent circumstance (50±5 % humidity, 23±1°C). The animals had free access to standard laboratory chow and enough drinking water except in the course of brief test periods. Behavioral experiment procedures were fulfilled between 9:00 a.m. and 2:00 p.m. All of the experiments and methods qualified in this research were performed in accordance with the Guidelines for the Care and Use of Laboratory Animals (National Institutes of Health Publication No.80-23, revised 1996) and were confirmed by research and ethics committee of Tehran Medical Sciences, Islamic Azad University, Tehran, Iran, ethical code 1401.074.

Regarding anesthetization, the rats received Ketamine Hydrochloride (80 mg/kg) plus Xylazine (20 mg/kg) with intraperitoneal (i.p.) injection to implicate adequate depth of anesthesia for surgical flow in stereotaxic equipment (machinery). In the next step, stainless steel guide cannula (27 guage,10 mm in length) was directed toward their dorsal third ventricle(D3V) (coordinates: anteroposterior (AP): -1.08 mm in comparison to bregma, mediolateral(ML): 0 mm and dorsoventral(DV): -5.2 mm from the skull surface) [23]. The injector cannula (22 gauge, 11 mm) was embedded into guide cannula and was anchored with dental acrylic cement. Drugs (Chloroquine diphosphate and Sulpiride) with 5λ volume were inject while the rat freely moved around the holding cage for over 2 minutes. All the rats experienced the recovery procedure at least 3-7 days after stereotaxic surgery. Microinjection process was performed by 22-guage needle connected to a short piece of polyethylene tube and a 25-µl Hamilton syringe. Morphine sulfate

was purchased from TEMAD (Tehran, Iran). Chloroquine diphosphate salt and Sulpiride were acquired from Sigma-Aldrich (St. Louis, MO, USA). The rats received daily intracerebroventricular (i.c.v.) injection of Chloroquine diphosphate (50 mM) for 4 continuous days (5 µl/day). Sulpiride was dissolved in vehicle (a drop of acetic acid in saline (p^H =7.4) immediately before the experiment. Sulpiride administration was performed in accordance with previous researches in the sense that we prepared 0.25(µg/rat) dose for (i.c.v.) injection.

For Morphine dependency, rats of addicted groups received the level of daily intake of morphine through oral administration in order to prevent stress of injection. We added 0.1 mg/ml morphine to drinking water on the first and second days of testing. 0.2 mg/ml was added on the third and fourth days; 0.3 mg/ml was added on the fifth and sixth day. On days seven through 21, the dose of morphine was fixed and we added 0.4 mg/ml morphine during this period (from the seventh to the 21st days). In addition to changing the bitter taste of morphine, Sucrose (20 mg/ml) was added into drinking water. This method of morphine administration has the Has advantage that morphine consumption is distinguished by the animal itself not by the examiner [24].

In this research, the animals were put in two separate tentative groups. First, the main group was Non-Addicted one including 32 rats, which was subdivided into four subgroups: subgroup Ia (including eight rats that received 5λ normal Saline (Control group), subgroup Ib (entailing eight rats that received 5λ Sulpiride) [25], subgroup Ic (comprising eight rats that received 5λ Chloroquine) and subgroup Id (including eight rats that received both Chloroquine and Sulpiride each of which contained 5λ volume).

The second main group was the addicted group including 32 rats, which was subdivided into four subgroups: subgroup IIa (entailing eight rats that consumed Morphine through oral administration), subgroup IIb (including eight rats that consumed Morphine through oral administration and received 5λ Sulpiride), subgroup IIc (comprising eight rats that consumed morphine through oral administration and received 5λ Chloroquine), and subgroup IId (including eight rats that consumed Morphine through oral administration and received both of Chloroquine and Sulpiride each of which 5λ volume). All injections of Chloroquine and Sulpiride were administered through (i.c.v.) injection. For addicted groups (group IIc and IId) receiving chloroquine, we injected 5λ Chloroquine (50mM) in their D3V for four continuous days (one injection/day) from the eighteenth day to the twenty-first day after starting morphine dependency. On the day of testing Id and IId groups, 10 mins after Chloroquine injection, Sulpiride was inject and 30 mins after Sulpiride injection, behavioral test was taken from the rats.

Learning and memory test

For assessing the level of learning and the memory of rats, the rats were given the shuttle box test. This instrument contains two compartments; each part size is (20×20×30 cm^3). For this experiment, the rats were allowed to acclimatize For 2 continuous days, before the test day, rats were transfer to test room for acclimatization. For gain (inception) train, the animals were put in the elucidated (transparent) chamber (cubicle) and 5 seconds later the guillotine door (7×9 cm^3) was picked up. Then, when all the four paws of rats crossed to the dark room, the guillotine door was closed and immediately an electric shock with 50 Hz frequency and 1 milliampere (mA) direct current was applied for 3 seconds. The rat exited the dark room after 20 seconds and was put temporarily into its cage. Two minutes after this process, we retested the rat in the same way as the pristine trials. If the rat stayed in the illuminated compartment for 120 seconds, successful acquirement of passive avoidance response was registered and training was ended. If the rat was not learning in first time, the process was repeated once again (up to three times for learning procedure with the interval of 30 minutes). The rat was put in the lighted room after 24 h of PA training and 5 seconds later, the guillotine door was opened for 5 mins. The latency of entering the dark room (Step-Through Latency =STL), Dark Room Entries (DAE) and Dark Room Time (DRT) were recorded.

Western Blotting

For investigating the effect of morphine addiction, autophagy inhibition and sulpiride injection (dopamine D2 antagonist) mitochondrial biogenesis western blotting was used for master regulation of mitochondrial biogenesis PGC-1α as described below:

Hippocampus, which has an important role in learning and memory, was extracted immediately after behavioral test and was stored in nitrogen tank for 24 hours; then, they were transported to minus 80˚C refrigerator, up to protein extraction for Western blotting test. Protein concentration was determined by spectrophotometer (Picodrop, UK). Sixty µgs of total protein in each sample were loaded and separated by SDS-PAGE and electrophoretically transferred onto polyvinylidene fluoride (PVDF) membranes. Electroblotted proteins were put onto PVDF

membranes after blocking with skim milk, probed with PGC-1α antibody overnight at 4 °C and then incubated with relevant secondary antibodies. Following extensive washing, immunoreactivity was visualized using the enhanced chemiluminescence method. Also, antibody was used against Beta-Actin as housekeeping protein to normalize all of the treatments. The bands were analyzed by densitometric quantification using ImageJ software and normalized to the appropriate loading controls.

Statistical analysis

All data were expressed as mean ± S.E.M and analyzed using one-way analyses of variance (ANOVA) with Graphpad Prism Software. Following Tukey's post-hoc analysis was performed for multiple comparisons. Differences with $p<0.05$ between tentative groups were accepted statistically.

3. Results

In this experiment, we evaluated the effects of morphine-dependence on learning and memory with shuttle box apparatus.

Effect of Morphine-dependence, Sulpiride and Chloroquine injection on Dark Room Entries (DRE) value

Fig. 1 shows the effect of pre-training Morphine oral administration and (i.c.v.) injection of Sulpiride and Chloroquine on Dark Room entries (DRE) in Shuttle box apparatus. Statistical analysis (One-way ANOVA and post hoc) indicated 18% decrease in dark room entries in the Chloroquine group and also Sulpiride+Chloroquine compared to the control group. Dark room entries decreased 34% in morphine+ Chloroquine group compared to the morphine group. In morphine+ Chloroquine+ Sulpiride group, it was 17% less than that in the morphine group.

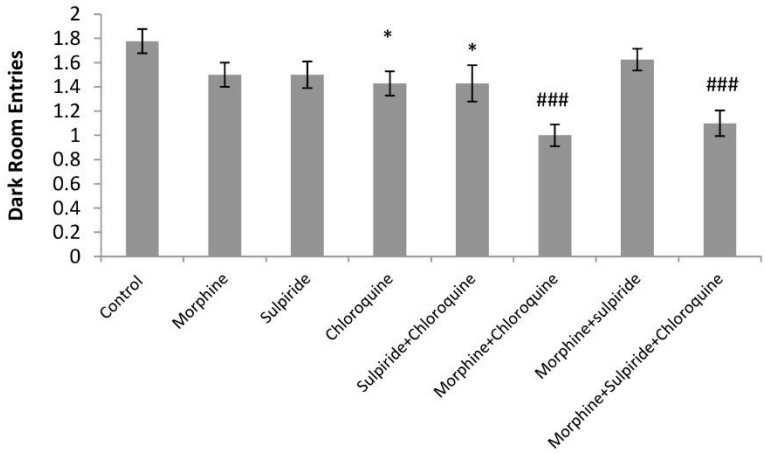

Fig. 1. The Effect of pre-training Morphine oral administration and (i.c.v.) injection of Sulpiride and Chloroquine on Dark Room Entries (DRE) value in passive avoidance learning test. Dark Room Entries (DRE) was measured for each animal. The test was taken 24 h after training. Each value expressed as mean ± S.E.M. In accordance with bahavioral protocol, eight animals were put per group. .$^{###}p$ <0.001 compared to the Morphine group. .$^{*}p$ <0.05 compared to the control group

Effect of morphine-dependence Sulpiride and Chloroquine injection on Dark Room Time (DRT) value

Fig. 2 illustrates the effect of pre-training Morphine oral administration and (i.c.v.) injection of Sulpiride and Chloroquine on Dark Room Time (DRT) in Shuttle box apparatus. Statistical analysis demonstrated a considerable difference in Dark Room Time (DRT) in the Chloroquine groups compared to that in the Control group (29% decrease).

The Sulpiride+ Chloroquine+morphine group showed 19% decrease, and the Sulpiride+ morphine group showed 11% decrease; Chloroquine+morphine demonstrated 22% decrease compared to the morphine group in (DRT) value.

Effect of morphine-dependence Sulpiride and Chloroquine injection on Step-Through Latency (STL)

Fig. 3 indicates the effect of pre-training morphine oral administration and (i.c.v.) injection of Sulpiride and Chloroquine on Step-Through Latency (STL) in Shuttle

box apparatus. Statistical analysis demonstrated a remarkable increase in the Chloroquine group compared to the Control group. Accordingly, the Chloroquine group had a notable increase 3.205 fold and the group receiving Sulpiride + Chloroquine had a significant increase 2.008 fold compared to the Control group. No considerable differences were observed in other experimental groups.

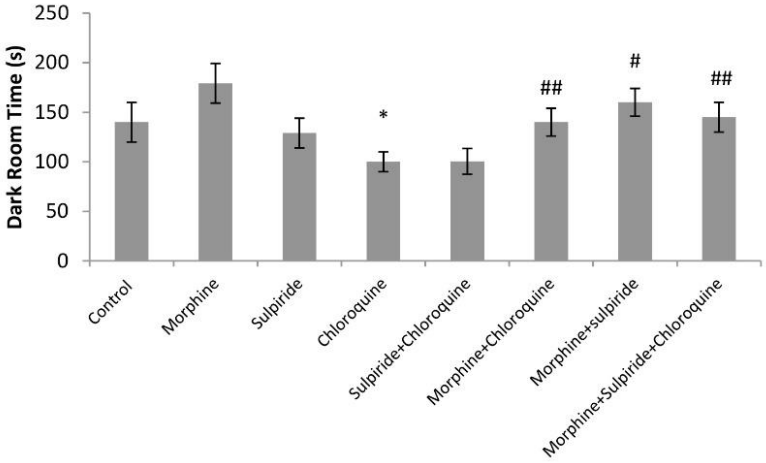

Fig. 2. The Effect of pre-training Morphine oral administration and (i.c.v.) injection of Sulpiride and Chloroquine on Dark Room Time (DRE) in passive avoidance learning test. Four groups received Morphine through oral administration(21 day). Sulpiride (0.25 µg/rat) and Chloroquine with 50 mM density(dose) were injected . Dark Room Time (DRE) was measured for each animal. The test was taken 24 h after training. Each value expressed as mean ± S.E.M. In accordance with bahavioral protocol, eight animals were put per group. # and *p <0.05 compared to the Control group(*) or the Morphine group(#).##p <0.01 compared to the Morphine group.

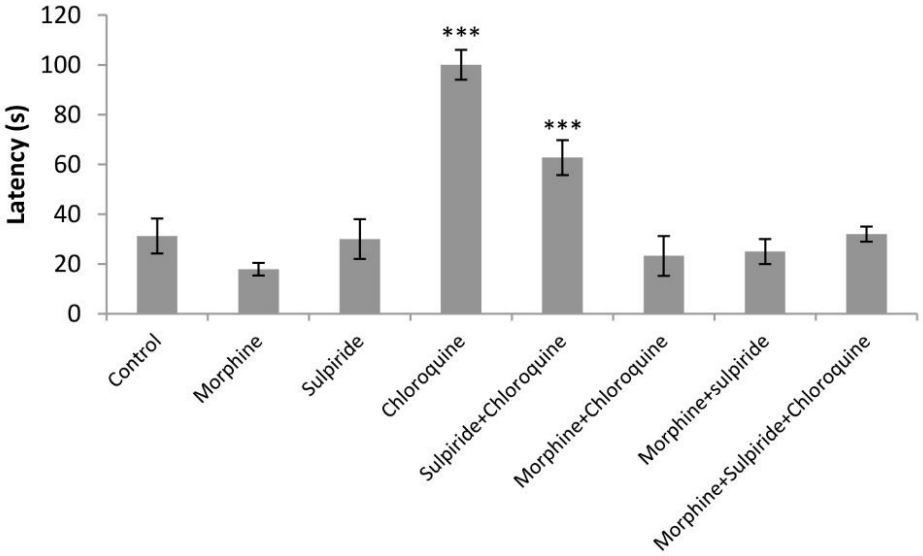

Fig. 3. The Effect of pre-training Morphine (oral administration)and i.c.v. injection of Sulpiride and Chloroquine on Step-Through Latency in passive avoidance learning test. Four groups received Morphine through oral administration(21 day). Sulpiride (0.25 µg/rat) and Chloroquine with 50 mM density(dose) were injected .The test was taken 24 h after training. Each value expressed as mean ± S.E.M. In accordance with bahavioral protocol, eight animals were put per group. ***p <0.001 compared to the Morphine group.

Effect of morphine-dependence Sulpiride and Chloroquine injection on PGC-1α protein level

Protein level of PGC-1α in rats which received Chloroquine was increased about 3 fold (***P<0.001) and also it was increased about 2 folds in the morphine group compared to the control group (***P<0.001). In group which received morphine and Chloroquine together, it was 1.3 folds more than that in the morphine group and also it was about 1.5 folds more in the group which received morphine+ Chloroquine+ Sulpiride (Fig 4).

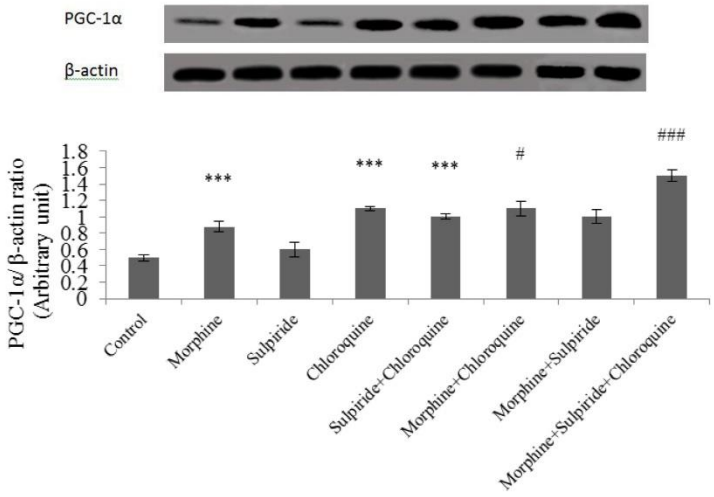

Fig. 4. Sixty micro gram of proteins were separated on SDS-PAGE, Western blotted, probed with anti- PGC-1α antibody, and re-probed with anti-b-actin antibody (one representative Western blot was shown). The densities of corresponding bands were measured and the ratio to b-actin bands was reported. Three rats were used for groups, and experiment was repeated 3 times independently. ***p <0.001 compared to the Control group. ### p <0.001 compared to the Morphine group. # p <0.05 compared to the Morphine group.

4. Discussion

According to previous studies on the effects of morphine oral administration on learning, According to previous studies on the adverse effects of morphine on learning, memory and cognitive abilities. [26, 27]. According to current results, morphine oral administration reduced learning and memory-like behavior in the sense that Dark Room Time (DRT) increased and Step-Through Latency (STL) decreased in the passive avoidance response. However, no considerable change in Dark Room Entries (DRE) was observed. In addition, the results of the present study indicated significant changes in groups receiving Chloroquine and Sulpiride. On the other hand, it was observed that pre-training (i.c.v.) injection of Chloroquine and Sulpiride (in the Chloroquine and Sulpiride groups), reduced Dark Room Time (DRT) and increased Step-Through Latency (STL) in the passive avoidance task in contrast to the effects of morphine addiction. Based on the findings of the present study, Chloroquine and Sulpiride enhanced the learning and memory-like behavior in comparison to morphine oral administration. Also, the effect of morphine-dependence Sulpiride and Chloroquine injection on PGC-1α protein level as a key regulator of mitochondrial biogenesis was investigated. PGC-1α protein level in rats which received Chloroquine and also in the morphine group increased and there was a more significant increase in rats which received morphine, Chloroquine and Sulpiride altogether.

A previous experiment about the effects of drug abuse, like morphine, on learning and memory revealed that post-training subcutaneous (s.c.) administration of morphine dose-dependently impairs learning and causes amnesia [28].

This result might be consistent with other reported data which have demonstrated that perpetuated administration and disuse (withdrawal) of addicted drugs modify the expression of various genes in the brain [29].

Moreover, one of the most important and vital factors associated with long-term memory and neurogenesis is correct function of mitochondria. Morphine has an adverse effect on mitochondrial function and could

induce apoptosis [30]. Lysosomal and Mitochondrial functions have an important role in cell survival and anti-oxidative defence system; when one of them undergoes some dis function, other would change its activity to reduce cellular problems [31]. Relation among mitochondrial function and lysosomal function is regulated with some factors involving PPARGC1 family of transcriptional co-activators [31, 33]. In the current study, using Chloroquine and sulpiride in morphine addicted rats increased mitochondrial biogenesis which could suggest its protective role in oxidative stress induced by morphine.

The effect of sulpiride on morphine-dependent learning has been described before [33], but in this study co-administration of sulpiride and lysosome inhibitor Chloroquine showed new insight in molecular mechanism of morphine addiction therapies; this suggests that accurate doses of these drugs could be used together to inhibit morphine-dependent impairments.

5. Conclusion

In conclusion, current data shows morphine has an adverse effect on learning and memory as it has been shown with spending more time in dark rooms of Shuttle box apparatus, which was reversed by Chloroquine (lysosomal inhibitor) and dopamine inhibitor (Sulpiride). Increasing PGC-1α protein level may suggest an important role of mitochondrial biogenesis in morphine-dependent learning changes. Overall, data suggest an important role of dopaminergic system along with lysosome and mitochondrial activity in morphine addiction status. More investigation is needed to understand signaling pathways underlying morphine addiction.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. This study was approved by the Ethics Committee of the Tehran Medical Sciences, Islamic Azad University (code 1401.074).

Funding

This work was funded by Tehran Medical Sciences, Islamic Azad University.

Author's contributions

The authors equally contributed to preparing this article.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

We would like to extend our appreciation and thanks to Tehran Medical Sciences, Islamic Azad University.

References

[1] Nestler EJ. Cellular basis of memory for addiction. Dialogues in clinical neuroscience; 2013.

[2] Taylor SB, Lewis CR, Olive MF. The neurocircuitry of illicit psychostimulant addiction: acute and chronic effects in humans. Subst Abuse Rehabil. 2013; 4:29-43. [DOI:10.2147/SAR.S39684] [PMID]

[3] Motaghinejad M, Ebrahimzadeh A, Shabab B. Preventive effect of central administration of venlafaxine on morphine physical dependence, nociception, and blood cortisol level in rat. Int J Prev Med. 2014; 5(11):1422-31. [PMID] [PMCID]

[4] Allan L, Hays H, Jensen NH, de Waroux BL, Bolt M, Donald R, et al. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. Bmj. 2001; 322(7295):1154. [DOI:10.1136/bmj.322.7295.1154] [PMID] [PMCID]

[5] Swendsen JD, Merikangas KR. The comorbidity of depression and substance use disorders. Clin Psychol Rev. 2000; 20(2):173-89. [DOI:10.1016/s0272-7358(99)00026-4] [PMID]

[6] Compton WM, Cottler LB, Ben Abdallah A, Phelps DL, Spitznagel EL, Horton JC. Substance dependence and other psychiatric disorders among drug dependent subjects: race and gender correlates. Am J Addict. 2000; 9(2):113-25. [DOI:10.1080/10550490050173181] [PMID]

[7] Curran HV, Kleckham J, Bearn J, Strang J, Wanigaratne S. Effects of methadone on cognition, mood and craving in detoxifying opiate addicts: a dose-response study. Psychopharmacology. 2001; 154:153-60. [DOI:10.1007/s002130000628] [PMID]

[8] Motaghinejad M, Ghaleni MA, Motaghinejad O. Preventive effects of forced exercise against alcohol-induced physical dependency and reduction of pain perception threshold. Int J Prev Med. 2014; 5(10):1299-307. [PMID] [PMCID]

[9] Motaghinejad M, Karimian M, Motaghinejad O, Shabab B, Yazdani I, Fatima S. Protective effects of various dosage of Curcumin against morphine

induced apoptosis and oxidative stress in rat isolated hippocampus. Pharmacol Rep. 2015; 67:230-5. [DOI:10.1016/j.pharep.2014.09.006] [PMID]

[10] Ferrer-Alcón M, J. García-Fuster M, La Harpe R, García-Sevilla JA. Long-term regulation of signalling components of adenylyl cyclase and mitogen-activated protein kinase in the pre-frontal cortex of human opiate addicts. J Neurochem. 2004; 90(1):220-30. [DOI:10.1111/j.1471-4159.2004.02473.x] [PMID]

[11] Narita M, Ioka M, Suzuki M, Narita M, Suzuki T. Effect of repeated administration of morphine on the activity of extracellular signal regulated kinase in the mouse brain. Neurosci Lett. 2002; 324(2):97-100. [DOI:10.1016/s0304-3940(02)00141-6] [PMID]

[12] Do Couto BR, Aguilar MA, Rodriguez-Arias M, Minarro J. Long-lasting rewarding effects of morphine induced by drug primings. Brain Res. 2005; 1050(1-2):53-63. [DOI:10.1016/j.brainres.2005.05.023] [PMID]

[13] Muller DL, Unterwald EM. In vivo regulation of extracellular signal-regulated protein kinase (ERK) and protein kinase B (Akt) phosphorylation by acute and chronic morphine. J Pharmacol Exp Ther. 2004; 310(2):774-82. [DOI:10.1124/jpet.104.066548] [PMID]

[14] Lin X, Wang Q, Ji J, Yu LC. Role of MEK-ERK pathway in morphine-induced conditioned place preference in ventral tegmental area of rats. J Neurosci Res. 2010; 88(7):1595-604. [DOI:10.1002/jnr.22326] [PMID]

[15] Nasehi M, Mafi F, Ebrahimi-Ghiri M, Zarrindast MR. Function of opioidergic and dopaminergic antagonists on both spatial and object novelty detection deficits induced in rodent model of hepatic encephalopathy. Behav Brain Res. 2016; 313:58-66. [DOI:10.1016/j.bbr.2016.07.011] [PMID]

[16] Voulalas PJ, Ji Y, Jiang L, Asgar J, Ro JY, Masri R. Loss of dopamine D1 receptors and diminished D1/5 receptor-mediated ERK phosphorylation in the periaqueductal gray after spinal cord lesion. Neuroscience. 2017; 343:94-105. [DOI:10.1016/j.neuroscience.2016.11.040] [PMID]

[17] Brami-Cherrier K, Valjent E, Garcia M, Pages C, Hipskind RA, Caboche J. Dopamine induces a PI3-kinase-independent activation of Akt in striatal neurons: a new route to cAMP response element-binding protein phosphorylation. J Neurosci. 2002; 22(20):8911-21. [DOI:10.1523/JNEUROSCI.22-20-08911.2002] [PMID]

[18] Acquas E, Pisanu A, Spiga S, Plumitallo A, Zernig G, Chiara GD. Differential effects of intravenous R, S-(±)-3, 4-methylenedioxymethamphetamine (MDMA, Ecstasy) and its S (+)-and R (−)-enantiomers on dopamine transmission and extracellular signal regulated kinase phosphorylation (pERK) in the rat nucleus accumbens shell and core. J Neurochem. 2007; 102(1):121-32. [DOI:10.1111/j.1471-4159.2007.04451.x] [PMID]

[19] Yoon S, Baik JH. Dopamine D2 receptor-mediated epidermal growth factor receptor transactivation through a disintegrin and metalloprotease regulates dopaminergic neuron development via extracellular signal-related kinase activation. J Biol Chem. 2013; 288(40):28435-46. [DOI:10.1074/jbc.M113.461202] [PMID]

[20] Yoon S, Choi MH, Chang MS, Baik JH. Wnt5a-dopamine D2 receptor interactions regulate dopamine neuron development via extracellular signal-regulated kinase (ERK) activation. J Biol Chem. 2011; 286(18):15641-51. [DOI:10.1074/jbc.M110.188078] [PMID]

[21] Dodds CM, Clark L, Dove A, Regenthal R, Baumann F, Bullmore ET, et al. Sulpiride modulates striatal BOLD signal during the manipulation of information in working memory. Pharmacopsychiatry. 2009; 207(1):35-45. [DOI:10.1007/s00213-009-1634-0] [PMID] [PMCID]

[22] van Rooijen G, Vermeulen JM, Ruhé HG, de Haan L. Treating depressive episodes or symptoms in patients with schizophrenia. CNS Spectr. 2019; 24(2):239-48. [DOI:10.1017/S1092852917000554] [PMID]

[23] Watson C. The rat brain in stereotaxic coordinates: hard cover edition. Academic press; 2007.

[24] Hoseinian M, Jalali TH, Ashabi G, Khalifeh S, Kheradmand A. The Effect of Maternal Morphine Addiction on Neural Plasticity of Fetal Brain in Wistar Rats. Qom Univ Med Sci J. 2022; 15(10):718-25.

[25] Khalifeh S, Khodagholi F, Zarrindast MR, Alizadeh R, Asadi S, Mohammadi Kamsorkh H, et al. Altered D2 receptor and transcription factor EB expression in offspring of aggressive male rats, along with having depressive and anxiety-like behaviors. Int J Neurosci. 2021; 131(8):789-99. [DOI:10.1080/00207454.2020.1758086] [PMID]

[26] Zarrinkalam E, Heidarianpour A, Salehi I, Ranjbar K, Komaki A. Effects of endurance, resistance, and concurrent exercise on learning and memory after morphine withdrawal in rats. Life Sci. 2016; 157:19-24. [DOI:10.1016/j.lfs.2016.05.034] [PMID]

[27] Sarkaki A, Assaei R, Motamedi F, Badavi M, Pajouhi N. Effect of parental morphine addiction on hippocampal long-term potentiation in rats offspring. Behav Brain Res. 2008; 186(1):72-7. [DOI:10.1016/j.bbr.2007.07.041] [PMID]

[28] Khajehpour L, Rezayof A, Zarrindast MR. Involvement of dorsal hippocampal nicotinic receptors in the effect of morphine on memory retrieval in passive avoidance task. Eur J Pharmacol. 2008; 584(2-3):343-51. [DOI:10.1016/j.ejphar.2008.02.030] [PMID]

[29] Lin X, Wang YJ, Li Q, Hou YY, Hong MH, Cao YL, et al. Chronic high-dose morphine treatment promotes SH-SY5Y cell apoptosis via c-Jun N-terminal kinase-mediated activation of mitochondria-dependent pathway. FEBS J. 2009; 276(7):2022-36. [DOI:10.1111/j.1742-4658.2009.06938.x] [PMID]

[30] Cunha-Oliveira T, Silva L, Silva AM, Moreno AJ, Oliveira CR, Santos MS. Acute effects of cocaine, morphine and their combination on bioenergetic function and susceptibility to oxidative stress of rat liver mitochondria. Life Sci. 2013; 92(24-26):1157-64. [DOI:10.1016/j.lfs.2013.04.016] [PMID]

[31] Salazar G, Cullen A, Huang J, Zhao Y, Serino A, Hilenski L, et al. SQSTM1/p62 and PPARGC1A/PGC-1alpha at the interface of autophagy and vascular senescence. Autophagy. 2020; 16(6):1092-110. [DOI:10.1080/15548627.2019.1659612] [PMID]

[32] Rabinovich-Nikitin I, Rasouli M, Reitz CJ, Posen I, Margulets V, Dhingra R, et al. Mitochondrial autophagy and cell survival is regulated by the circadian Clock gene in cardiac myocytes during ischemic stress. Autophagy. 2021; 17(11):3794-812. [DOI:10.1080/15548627.2021.1938913] [PMID]

[33] Zarrindast MR, Bananej M, Khalilzadeh A, Fazli-Tabaei S, Haeri-Rohani A, Rezayof A. Influence of intracerebroventricular administration of dopaminergic drugs on morphine state-dependent memory in the step-down passive avoidance test. Neurobiol Learn Mem. 2006; 86(3):286-92. [DOI:10.1016/j.nlm.2006.04.002] [PMID]