

Single and Repeated Ultra–Rapid Detoxification Prevents Cognitive Impairment in Morphine Addicted Rats: A Privilege for Single Detoxification

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Original Article

Abstract

Background: Opioids have been shown to affect learning and memory processes. Different protocols of morphine withdrawal can substantially vary in their success to prevent opioid induced impairments of cognitive performance. In the present study, we report the effects of single and repetitive ultra-rapid detoxification (URD) on spatial learning and memory in morphine addicted rats.

Methods: Morphine (10 mg/kg) was intraperitoneally (IP) injected in male rats once a day over one week and after which they were detoxified with naloxone administration under anesthesia. For the repetitive procedure, a second one week morphine treatment with a second subsequent detoxification was performed. Control groups received an equivalent volume of saline injections. Spatial learning and memory was evaluated using the Morris water maze (MWM) task.

Findings: Both protocols of morphine administration resulted in a severe spatial memory impairment that could be significantly prevented by both single and repetitive URD. However, memory abilities in animals treated with repetitive URD were still significantly lower than in animals of the corresponding control group. Alterations in motor activity or sensory-motor coordination between morphine treated and control animals could be ruled out by comparing swimming speed and visible platform performances that were not different between groups. Thus, URD and, specifically single URD, can prevent the spatial memory impairments in addicted rats.

Conclusion: As opioid addiction is an extending and serious concern in many societies, these findings may have clinical values and therapeutic implications for patients who experience multiple opioid relapses.

Keywords: Opioid, Addiction, Detoxification, Spatial memory, Morris water maze (MWM)

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Introduction

Morphine, an alkaloid derived from opium poppy (*Papaver somniferum* plant) is one of the most potent analgesic substances that can also induce relaxation and euphoria.^{1,2} Due to these properties, all opioids (including morphine, heroin, and some of the prescription analgesics) have extremely high abuse potential. Dependence on these drugs has been associated with many health and social problems, such as increased risk for HIV, mortality, crime, unemployment, and interpersonal breakdowns.² For these reasons, opioid addiction has been defined as a “chronic, relapsing disease” and has turned into a substantial public health concern.³

Opioids play a key role in cognitive performances.⁴ Previous human and animal studies have shown that morphine and other opioidergic agents can modulate learning and memory processes, either in positive or negative directions.⁵⁻⁸ The reported inconsistencies may be due to different experimental conditions, protocols, and species used, and also variation in the dosage, route, and in particular the duration of the drugs administration. For example, acute or chronic opioid treatment has been shown to have different influences on memory function.⁵⁻⁸ Some studies have demonstrated that pre-training administration of morphine leads to the inhibition of memory acquisition in different paradigms such as Y-maze discrimination, active or passive avoidance, and operant tasks.^{6,9-11} In the case of the chronic administration, learning deficits have been reported in the Morris water maze (MWM) paradigm.^{7,8} In a study by McNamara and Skelton, it has been reported that repeated exposure to morphine impairs acquisition, but not memory consolidation in water maze task.⁷

Evidences propose that opioid-induced memory impairment is mediated by the activation of mu-opioid receptors while such deficits can be reversed by the mu-receptor antagonist naloxone.¹²⁻¹⁴ It has been shown that morphine-induced memory deficit is immediately reversed by naloxone, indicating that the restoration of memory function by naloxone is mediated by the blockade of mu-receptors.^{8,15}

The traditional protocols of opioid detoxification were based on substituting the opioids with a long acting drug, such as methadone, and then tapering

its dose.^{16,17} Such methods are too long and patients usually suffer from a severe withdrawal symptom.¹⁸ However, in rapid and ultra-rapid detoxification (RD and URD) in which opioid antagonists are administered alone or under general anesthesia, respectively, the withdrawal signs and syndrome are alleviated and precipitated in a quite short period of time (5-8 hours).¹⁹⁻²²

Some studies have reported the deleterious effects of methadone (a substance used as a traditional detoxification agent) on cognitive abilities of opioid-addicted subjects.²³⁻²⁶ There are also several findings revealing the reversal effect of RD with naloxone on memory impaired opioid addicted animals.^{8,27,28} In addition, existing studies show that multiple detoxifications of some abused substances, like alcohol, can affect the cognitive functions of addicted subjects.^{29,30}

Although a considerable body of scientific literature has investigated the effects of different protocols of detoxification on cognitive abilities, to date and to our knowledge, no study has been done to evaluate the effects of single and repeated detoxification on memory performance of morphine addicted rats under anesthesia URD. Therefore, since the repeated relapses to opioid abuse and subsequent detoxification in addicted patients have become a serious concern in many societies, we decided to examine the effects of single and repeated URD on spatial learning and memory of morphine addicted rats.

Methods

Adult male rats weighing 200-250 g were obtained from the animal house of Kerman Neuroscience Research Center (Kerman, Iran). The animals were housed under standard conditions of light (12 h light-dark cycle, lights on 07:00-19:00) and temperature (23 ± 1 °C). They were caged in groups of 4 and had free access to food and water. In this study, 2 sets of 3 groups of animals (control, morphine, and detoxification) were used for once and twice URD protocols ($n = 8$). All the experimental treatments and protocols were approved by the Ethical Committee of the Kerman Neuroscience Research Center (EC/KNRC/89/46). Morphine sulfate and naloxone hydrochloride were purchased from Temad and Tolid-Daru Pharmaceutical Companies (Tehran, Iran), respectively. Before injections, morphine sulfate was dissolved in sterile 0.9% saline and injected

intraperitoneally (IP).

Following 1 week of handling and habituation, the animals received IP injections of morphine or saline (10 mg/kg) once a day for 1 or 2 weeks.³¹ To ensure that the rats had become fully addicted, two additional rats were injected with naloxone (3 mg/kg IP) 5 h after the last injection of morphine on the seventh day, and then abdominal contraction, weight loss, diarrhea, ptosis, and teeth chattering were considered as the signs of drug addiction.³²

Ultra-rapid detoxification was performed 12 h following the last injection of morphine.³³ In this protocol, the rats were anesthetized with pentobarbital (120 mg/kg IP) for 4-5 h. The applied dose of pentobarbital was obtained by a pilot experiment in our lab. The first, second, and third naloxone injections (1 mg/kg sc) were accomplished at 10 min, 2 h and 10 min, and 4 h and 10 min intervals after the induction of anesthesia.³⁴ The described procedures of addiction and URD were exactly repeated for animals submitted to the twice URD. After complete recovery from anesthesia, the animals were placed in individual cages, and 14-16 h later, the behavioral test in MWM was performed. In control groups, saline was injected in the same way.

The MWM is one of the most widely used paradigms in behavioral neuroscience for assessing the potential effects of experimental manipulations on spatial learning and memory.³⁵ The device is a black circular tank (160 cm in diameter, 80 cm in height) filled with water maintained at room temperature to a depth of 40 cm. It is geographically divided into 4 equal quadrants (N, S, E, and W). A square platform (10 cm in diameter) is located 1.5 cm below the surface of the water in the center of the northeast quadrant. The experiments are performed in a dimly lit room with spatial cues (e.g., circles, squares, or triangles) attached at different points on the walls around the maze. A smart video tracing system (NoldusEthovision® system, version 5, USA) recorded the performances of rats which were traced on the screen of a computer.

After habituation to the MWM, each rat accomplished 3 blocks with 30 min resting time intervals. Each block consisted of 4 consecutive trials (60 s) and 3 60 s intertrial intervals with 4 different releasing points. On each trial, the rats were placed in the water facing toward the wall of

the quadrant where they were released (quadrant was selected randomly). After the animal found the platform, it was allowed to rest there for 20-30 s and was then transferred to an animal cage to wait 20-30 s before the start of the next trial. If the rat did not find the platform in 60 s, it was guided to the platform by the experimenter. The time and distance to find the hidden platform were the parameters of spatial learning. In this version of MWM, rats became fully trained in approximately 3 h. During the acquisition, the platform was constant. In order to test the spatial memory in the water maze, a single-probe trial was given 2 h after the last training trial. In this trial rats were allowed to swim freely for 60 s in the pool without platform. The time and distance spent in the target quadrant (quadrant 4) were considered as the spatial memory retention. Following the probe trial, visible platform test was performed. The purpose of this test was to assess the health of sensory and motor coordination, or motivation and possible interference of the experimental interventions with the mentioned parameters. In this test, the ability of the animals to escape to a visible platform (platform was raised 2 cm above the water level and became visible with aluminum foil) was examined.^{36,37} All the experimental groups were tested between 10 AM and 12 AM.

To determine the differences in the learning rates among the groups, the time spent to find the platform in the MWM training was analyzed by two-way analysis of variance (ANOVA) with repeated measures (group and block as the factors). All comparisons among the groups for the data collected in the MWM probe trials, swim speed, and latency to visible platform were analyzed with one-way analysis of variance (ANOVA) followed by Tukey's post-hoc multiple comparison tests. Data are expressed as means \pm SEM (two-way repeated measure ANOVA and ANOVA without repeated measure followed by Tukey test). The statistical level of significance was considered as $P < 0.05$.

Results

Spatial Learning

As shown by decrease in escape latency (during acquisition, e.g. learning phase), the animals of all groups learned to find the hidden platform with subsequent blocks of trials. Repeated

measure analysis of ANOVA revealed no significant difference in escape latency block trials between saline, once rapid detoxification, and morphine groups (Figure 1). In the 2 weeks morphine group, however, escape latency in 3 blocks was significantly increased as compared to saline group (50.98 ± 8.7 , 41.27 ± 8.6 , and 33.97 ± 18.1 vs. 36.1 ± 5.7 , 18.44 ± 6.5 , and 12.93 ± 4.8 ; $P = 0.005$, $P = 0.001$, and $P = 0.006$ in block 1, 2, and 3, respectively; Figure 2). As shown in figure 2, the mean escape latency in block 1, 2, and 3 in the twice rapid detoxification group were

decreased compared to the morphine group (36.33 ± 10.1 , 25.72 ± 11.9 , and 17.79 ± 8.7 vs. 50.98 ± 8.7 , 41.27 ± 8.6 , and 33.97 ± 18.1 ; $P = 0.006$, $P = 0.008$, and $P = 0.03$ in block 1, 2, and 3, respectively). There were no significant differences in spatial learning between 1 and 2 weeks morphine treated groups as well as the once and twice detoxification groups (data not shown). These results show that the 2 weeks morphine treatment impairs the spatial learning and twice rapid detoxification can improve this impairment.

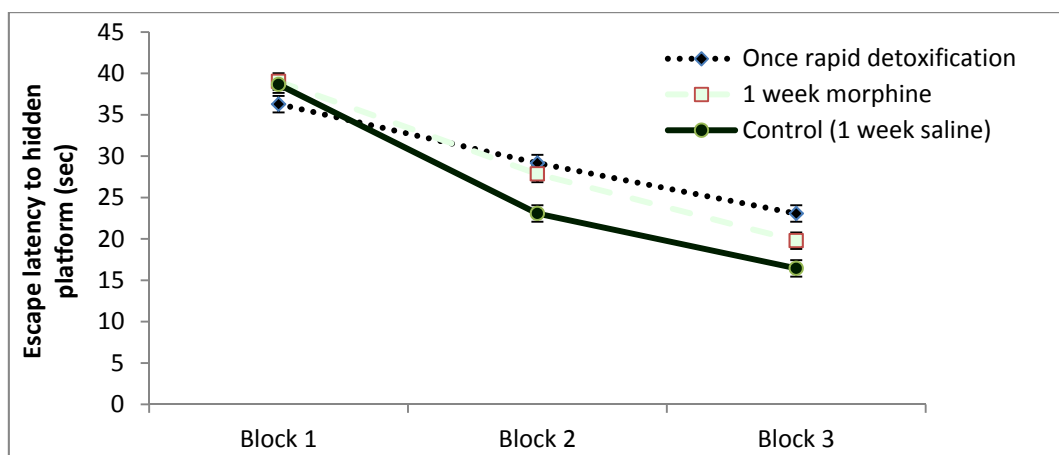


Figure 1. Effects of once URD (Ultra-rapid detoxification) on spatial learning in the Morris water maze (MWM). Each block represents the mean latency of four consecutive trials to find the hidden platform. One week of morphine treatment and once rapid detoxification did not lead to any significant difference in spatial learning. Data are shown as mean \pm SEM (two-way repeated measure ANOVA and ANOVA without repeated measure followed by Tukey test)

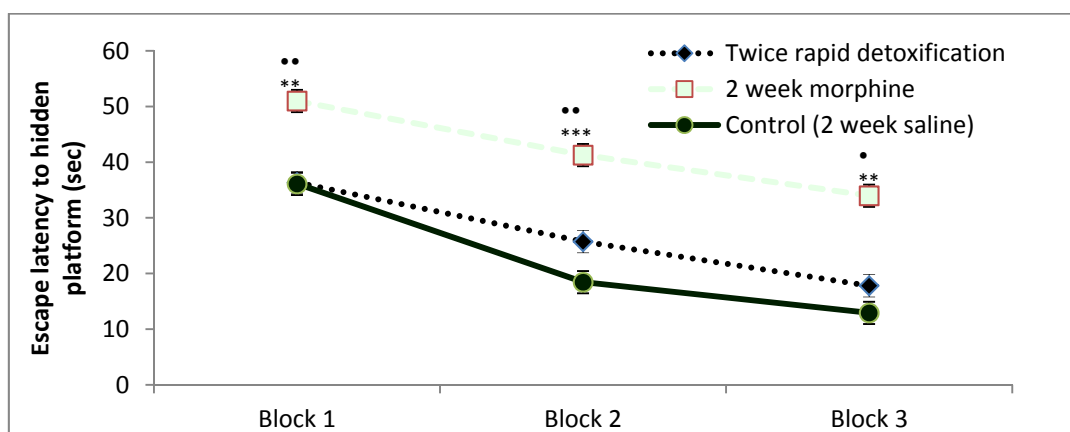


Figure 2. Effects of twice URD (Ultra-rapid detoxification) on spatial learning in the Morris water maze (MWM). Each block represents the mean latency of four consecutive trials to find the hidden platform. In comparison with control and twice rapid detoxification groups, mean latency in all three blocks was significantly increased in two weeks morphine treated rats. *** $P < 0.010$, **** $P < 0.001$ indicate the difference from the saline group. • $P < 0.050$, •• $P < 0.010$ indicated the difference from the twice rapid detoxification group. Data are shown as mean \pm SEM (two-way repeated measure ANOVA and ANOVA without repeated measure followed by Tukey test).

Spatial Memory

The results of the spatial memory test are shown in figures 3, and 4. The animals that received morphine for 1 and 2 weeks compared to their

control groups spent significantly less time and distance in the Q4 (target quadrant) (1 week morphine: $F_{(2,21)} = 24.5$, $P < 0.001$ for time, and $F_{(2,21)} = 24.06$, $P < 0.001$ for distance; 2 weeks

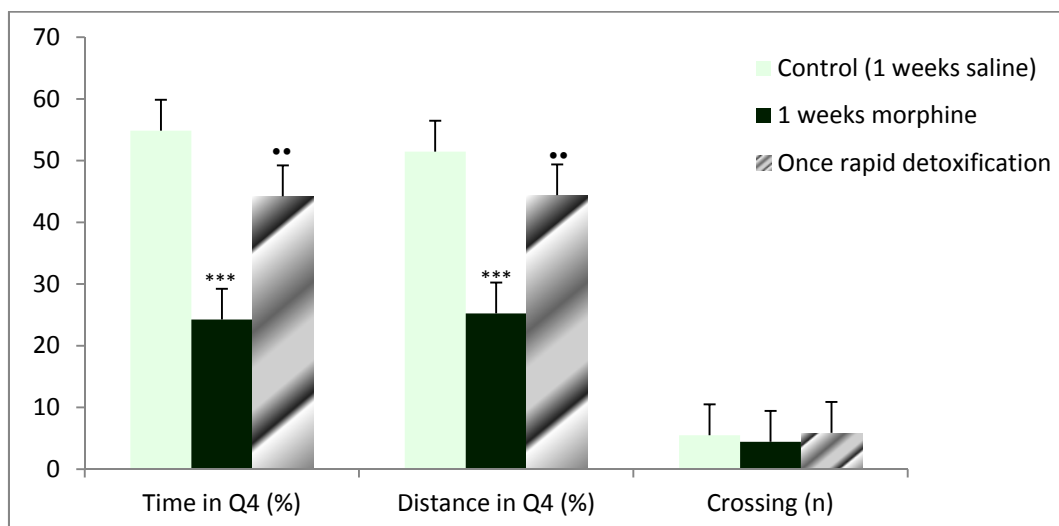


Figure 3. Effects of once URD (Ultra-rapid detoxification) on spatial short-term memory in the probe trial, 2 h after block 3 of training in the Morris water maze (MWM). Spatial memory is defined as the time and distance spent in the target quadrant as well as the number of crossing on this quadrant. The time and distance in target quadrant were decreased in the one week morphine treated rats. These parameters were increased in the once URD group. *** $P < 0.001$ indicated difference from saline group. ** $P < 0.010$, indicated difference from morphine group. Data are shown as mean \pm SEM (one-way ANOVA followed by Tukey test).

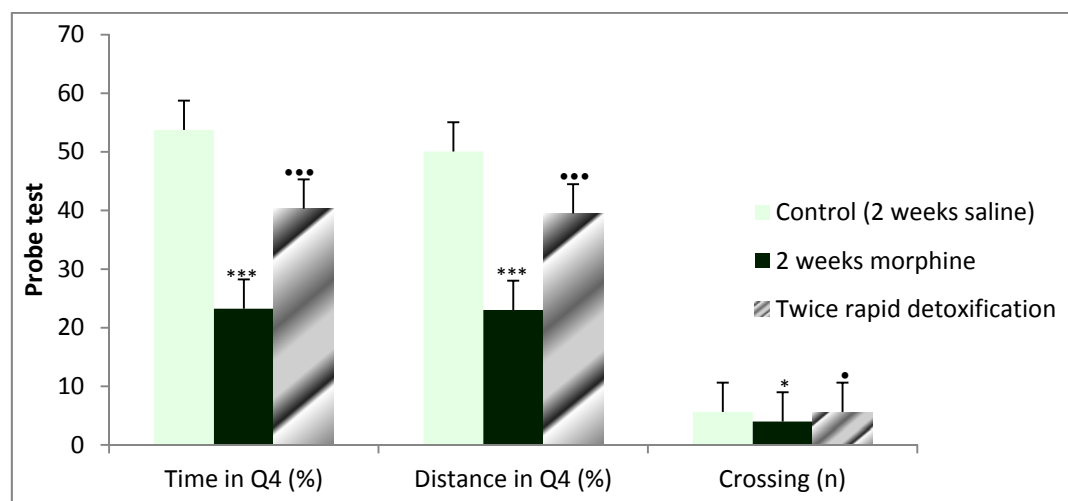


Figure 4. Effects of twice URD on spatial short-term memory in the probe trial, 2 h after block 3 of training in the Morris water maze (MWM). Spatial memory is defined as the time and distance spent in the target quadrant as well as the number of crossing on this quadrant. The time and distance in target quadrant were decreased in two weeks morphine treated rats. These parameters were increased in twice URD group; however, they were significantly lower than those in the saline group. Numbers of crossing on target quadrant in the two weeks morphine treated rats were also decreased compared to saline and twice rapid detoxification groups. * $P < 0.050$, ** $P < 0.010$ and *** $P < 0.001$, indicated difference from saline group. • $P < 0.050$ and ••• $P < 0.001$ indicated difference from morphine group. Data are shown as mean \pm SEM (one-way ANOVA followed by Tukey test).

morphine: $F_{(2,21)} = 33.9$, $P < 0.001$ for time, and $F_{(2,21)} = 40.67$, $P < 0.001$ for distance; Figures 3, and 4). As indicated in figure 3, the once treated rats spent significantly higher percentage of time and distance in Q4 than the rats which received morphine (time: $F_{(2,21)} = 24.5$, $P < 0.001$, distance: $F_{(2,21)} = 24.06$, $P < 0.001$). The difference between once URD and control groups was not significant (time: 44.22 ± 5.72 , and 54.86 ± 7.62 , distance: 44.39 ± 6.76 , and 51.46 ± 5.84 for URD and control groups, respectively). Spatial short-term memory parameters were better in twice detoxification group compared to the morphine group; however, they were worse than the control group (time: $F_{(2,21)} = 33.9$, $P < 0.001$; distance: $F_{(2,21)} = 40.67$, $P < 0.001$, Figure 4). The crossing numbers on target quadrant in 2 weeks morphine treated rats were fewer than the twice detoxification and control groups ($F_{(2,21)} = 4.65$, $P < 0.05$, Figure 4). These results suggest that 1 and 2 weeks of morphine treatment impair the spatial memory while twice and particularly once rapid detoxification can improve it significantly. There were no significant differences in the spatial memory between 1 and 2 weeks treated morphine groups (data not shown). The results of the swimming speed and visible platform did not show any significant differences between any of the 6 groups (Table 1). These results indicate that morphine treatment, once and twice rapid detoxification did not affect the swimming speed and latency to visible platform, suggesting that motor activity and sensory-motor coordination were not affected following these interventions.

Discussion

To our knowledge, this is the first report to document the mediation of cognitive functions following single and repeated URD in opioid

addicted rats. The extent of the effects of single and repeated URD with naloxone under pentobarbital anesthesia on spatial learning and short-term memory has been proved to be different. We found that IP administration of morphine for 1 week did not lead to any significant differences in spatial learning, whereas 2 weeks morphine treatment impaired learning ability and repetitive URD could improve this impairment in rats. Furthermore, both morphine application protocols severely disrupted spatial memory, and both URD protocols could prevent impaired memory performance. However, it seems that the improving effect of single URD on memory impairment is greater than that of repeated URD. Since there was no significant difference between the control (saline injected) and untreated groups in cognitive parameters (the data of the untreated groups are not presented), it is unlikely that injections have nonspecific effects on the observed differences in behavioral performance. Moreover, the results of the visible platform experiment and swimming speed suggest that morphine treatment and URD protocols have no significant effects on mood, motivation, and sensory-motor coordination of rats. Therefore, it seems reasonable to postulate that morphine disrupts the learning and memory function via its deleterious effects on the brain regions involved in memory processes such as hippocampus.

Morphine, a substance derived from the natural extract of the opium poppy, *papaver somniferum* plant, is considered as the most potent analgesic substance that can also induce relaxation and euphoria.^{1,2} Opioid receptors are distributed throughout the central nervous system (CNS) including the hippocampus, a region fundamental for encoding and retrieving of information.³⁸⁻⁴¹ It has been demonstrated that hippocampal mu-opioid receptors play an essential role in spatial learning and memory.⁴²

Table 1. Swimming speed and latency to visible platform

| Groups (n = 8) | Swimming speed (cm/s) | Latency to the visible platform (sec) |
|----------------------------|-----------------------|---------------------------------------|
| One week saline | 22.36 ± 1.47 | 13.18 ± 1.92 |
| One week morphine | 24.14 ± 0.44 | 16.00 ± 1.11 |
| Once rapid detoxification | 23.56 ± 0.75 | 5.65 ± 0.77 |
| Two weeks saline | 21.32 ± 1.40 | 15.34 ± 1.06 |
| Two weeks morphine | 23.27 ± 1.05 | 16.99 ± 2.82 |
| Twice rapid detoxification | 22.19 ± 0.72 | 13.53 ± 1.69 |

One way analysis of variance (ANOVA) was used for the comparison of swim speed and latency to visible platform in Morris water maze (the differences are not significant)

Data are means ± SEM for groups of 8 rats each

We applied the MWM paradigm, the most widely used behavioral paradigm, not only to assess the spatial memory, but also avoidance behavior and sensory-motor functions.⁴³ The results of a number of previous studies examining the effects of morphine and its naloxone induced withdrawal on cognitive performance in the MWM are in line with our study.^{8,44} Repeated or single pre-training morphine administration (5, 10, and 20 mg/kg) disrupted spatial learning of rats, as well as spatial memory formation and retention.^{7,8,45} Although, many studies have predominantly reported the negative effects of opioids on learning and memory capacities, there are a few evidence stating the enhancing effects of these substances on memory functions.^{5,13,46,47}

These slight inconsistencies may be due to different routes and doses of morphine exposure, or different behavioral tasks and species applied. The negative effects of opioids on cognitive abilities are mainly exerted through the mediation of mu-opioid receptors, since receptor blockade by naloxone, a specific antagonist of mu-receptors, can reverse these effects.^{8,12-14} The nature of this reversal is not yet well understood, but a variety of possible pathways have been described. Naloxone releases the medial septal cholinergic neurons from opiate inhibition and thus causes an increase in the release of acetylcholine in the hippocampus.^{48,49} In addition, blockade of endogenous opioid mechanisms can lead to elevated cyclic GMP (cGMP) production.⁵⁰ It is well confirmed that the cGMP-dependent protein kinase systems play an important role in memory consolidation.^{51,52}

Morphine withdrawal is associated with the activation of hypothalamus-pituitary-adrenal axis (HPA) and thus the elevation of plasma corticosterone level, which in turn can result in cognitive impairments through the effects on some signaling cascade molecules at hippocampal synapses that play critical roles in synaptic plasticity, and learning and memory.⁵³⁻⁵⁶

However, by inducing withdrawal by naloxone injection under anesthesia (URD) in our

experiment, it can be postulated that the probability of the elevation of stress level of the animals and subsequent structural, molecular, and functional changes in the brain are minimized. Therefore, the observed improving effects of URD on memory performance are very likely a consequence of change in stress level of animals; though more studies are needed to confirm this preliminary statement.

Based on the results of the present study, it seems that repetitive detoxification following repeated morphine addiction is less effective in rescuing memory functions compared to a single acute detoxification. This difference may be due, in part, to the deleterious effects of higher frequency of addiction and withdrawal processes which animals experience in the repeated URD group. Interestingly, these results are in agreement with findings of some human studies showing that patients who have a history of 2 or more alcohol detoxifications are more cognitively impaired than patients with only 1 or no previous detoxification.^{30,57} Given the limited set of data in this area, however, further studies are required, particularly in humans, to establish these initial observations.

Conclusion

We conclude that single URD at an early stage of morphine addiction would be a valuable protocol for addiction treatment in which the patients will experience milder withdrawal symptoms and may especially have therapeutic implications for those patients who experience multiple opioid relapses.

Conflict of Interests

The Authors have no conflict of interest.

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یک و دو بار سم‌زدایی به روش فراسریع از نواقص شناختی در موش‌های صحرایی معتاد به مورفین جلوگیری می‌کند: ارجحیت برای یک بار سم‌زدایی

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مقاله پژوهشی

چکیده

مقدمه: مشخص شده است که اپیوئیدها بر فرایندهای یادگیری و حافظه‌ای تأثیر می‌گذارند. تفاوت‌های مهمی در موفقیت روش‌های مختلف قطع مورفین برای جلوگیری از نواقص شناختی وجود دارد.

روش‌ها: در مطالعه حاضر اثرات یک و دو بار سم‌زدایی به روش فراسریع (Ultra-rapid detoxification یا URD) بر یادگیری و حافظه فضایی موش‌های صحرایی معتاد به مورفین بررسی شد. مورفین (۱۰ میلی‌گرم بر کیلوگرم) به صورت داخل صفاقی یک بار در روز به مدت یک هفته به موش‌های صحرایی نر تزریق شد و سپس تحت بیهوشی قرار گرفتند و به وسیله تزریق نالوکسان سم‌زدایی شدند. جهت پروتکل تکراری، تزریق مورفین و به دنبال آن فرایند سم‌زدایی یک هفته دیگر هم تکرار گردید. حیوانات گروه شاهد حجم‌های یکسانی از سالیان دریافت کردند. یادگیری و حافظه فضایی با استفاده از آزمایش MWM (Morris water maze) مورد بررسی قرار گرفت.

یافته‌ها: هر دو پروتکل منفرد و تکراری تجویز مورفین منجر به تضعیف شدید حافظه فضایی و هر دو روش سم‌زدایی به روش فراسریع منفرد و تکراری باعث بهبود نواقص شد. با این وجود عملکرد حافظه‌ای حیواناتی که دو بار URD را تجربه کرده بودند، در مقایسه با گروه شاهد متناظر خودش به طور معنی‌داری کمتر بود. از آنجایی که سرعت شنای حیوانات و همچنین نتایج آزمون سکوی آشکار بین گروه‌های شاهد و دریافت کننده مورفین تفاوت معنی‌داری را نشان نداد؛ می‌توان نتیجه‌گیری کرد که فعالیت حرکتی و یا هماهنگی حسی- حرکتی حیوانات مورد آزمایش تحت تأثیر تجویز مورفین قرار نگرفت.

نتیجه‌گیری: سم‌زدایی به روش فراسریع و به ویژه پروتکل یک روزه آن می‌تواند باعث بهبود نواقص شناختی در موش‌های معتاد به مورفین شود. با توجه به این‌که اعتیاد به مورفین یک معضل جدی و رو به گسترش در بسیاری از جوامع است، این نتایج می‌تواند برای بیمارانی که بازگشت‌های مکرر به مصرف اپیوئید را تجربه می‌کنند، اهمیت بالینی داشته باشد.

واژگان کلیدی: اپیوئید، اعتیاد، سم‌زدایی، حافظه فضایی، ماز آبی موریس (MWM)

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