

# Effects of Maternal Separation on Nicotine-Induced Conditioned Place Preference and Later Spatial Learning and Memory Function in Adolescent Male Rats

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## Original Article

### Abstract

**Background:** Disturbances in maternal care have been associated with increased risk for drug abuse later in life. However, there has been little investigation of the effects of maternal separation (MS), a model of early life stress, on nicotine dependence, specifically during adolescence. In the present study, we aimed to investigate the effect of MS on nicotine-conditioned place preference (CPP) in adolescent male rats. We also examined the impact of nicotine on spatial learning and memory impairments induced by MS.

**Methods:** Rat pups were exposed to daily MS for 15 (MS15) or 180 (MS180) minutes during the first 2 weeks of life or reared under normal animal facility rearing (AFR) conditions. In postnatal day (PND) 28-34, they were conditioned with nicotine [0.6 mg/kg, subcutaneously (SC)] or saline and tested for preference over a period of 6 conditioning trials. Morris water maze (MWM) testing was performed to assess spatial cognitive function.

**Findings:** The MS procedure used in our study failed to affect nicotine reward as measured by CPP in the adolescent male rats. Notably, significant spatial learning deficit was seen in the MS180 rats compared to those in the AFR and MS15 groups and nicotine administration modified the MS-induced learning defect in adolescent male rats.

**Conclusion:** In conclusion, although MS revealed no influence on the sensitivity to the nicotine's reinforcing effects in adolescent male rats, the simultaneous effect of MS on learning performance may be altered by nicotine intake.

**Keywords:** Separation; Nicotine; Spatial learning; Spatial memory; Rats

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## Introduction

Maternal separation (MS) is an animal model of early life stress which has been developed to study the effects of adverse early experiences on physiological and behavioral functions, including growth, metabolism, reproduction and inflammatory/immune responses.<sup>1</sup> Separation from mother, particularly if recurrent, induces persistent increase in anxiety-like behaviors, decreases exploratory locomotor response to novelty, disrupts dopaminergic and serotonergic activity, and causes deficits in learning and memory function and changes in the hypothalamic-pituitary-adrenal (HPA) axis responses to stressful stimuli in rat pups.<sup>2-5</sup> Furthermore, early postnatal stressful experiences such as MS have been shown to play a critical role in the acquisition, maintenance, and relapse of drug abuse in both animals and human beings.<sup>6,7</sup> Maternally separated animals show enhanced alcohol preference and intake, hypersensitivity to the reinforcing effects of morphine, enhanced acquisition of cocaine, and hypersensitized response to methamphetamine and cannabinoids.<sup>8</sup>

Based on the evidence in rodents, there is no information available about the role of MS in the vulnerability to nicotine addiction in experimental animal populations later in life. In addition, drug abuse among humans often begins during adolescence, a time of remarkable physical and behavioral change and ontogeny in which individual's exhibit age-specific behavioral properties such as risk taking and novelty seeking, which could prepare them to initiate drug use.<sup>9</sup>

Nicotine administration during adolescence causes resistance upregulation of nicotinic cholinergic receptors in rat brain regions; these subjects are more sensitive to the rewarding properties of nicotine as analyzed by self-administration and the conditioned place preference (CPP) procedures compared to adult subjects.<sup>10</sup>

In addition, MS has been repeatedly shown to affect multiple aspects of brain function, and is known to induce cognitive, emotional and neurochemical dysfunction in adult rats.<sup>4</sup> Contrary to the effects of MS, nicotine may enhance cognitive function by interaction with the presynaptic nicotinic acetylcholine receptors to

facilitate the release of several different neuromodulators that have been involved in learning and memory.<sup>11</sup>

However, there has been no study on the effect of nicotine administration on cognitive processes in adolescent animals neonatally exposed to MS. Therefore, the present study was designed to investigate the capability of male rat pups subjected to short (15 min) and prolonged (180 min) periods of separation in postnatal day (PND) 1-14 for the rewarding properties of nicotine using a place-preference conditioning procedure during adolescence. The respective MS group was also compared with animal facility reared (AFR) control rats. We also examined whether nicotine administration affects subsequent spatial learning and memory ability in adolescent male rats exposed to neonatal MS.

## Methods

**Animal:** Pregnant Wistar rats were obtained from the colony maintained by Neuroscience Research Center Animal House on gestational days 14-15.

They were housed under controlled illumination (12 h/12 h, lights on at 07:00 hours) and ambient temperature ( $23 \pm 1$  °C). Each pregnant female rat was individually accommodated with free access to both food and water. All the experimental protocols were approved by the ethical committee of Kerman Neuroscience Research Center (Ethics Code: KNRC-9-33), Iran. Experiment was done with 6-8 rats per group.

**MS treatment:** Pair-housed female rats were inspected twice a day for newborn litters. The birthday was considered to be PND0. Between PND1 and PND14, the separation protocol took place by the method described in Andersen et al.<sup>12</sup> and Weiss et al.<sup>13</sup>

All the MS180 pups were separated from their dams for 180 min from PND 1-14. As for the 15-minute MS (MS15) group, pups were exposed to 15 min of MS from PND 1-14.

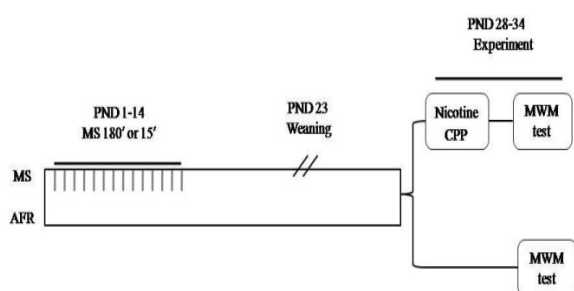
The manipulation of the pups was initiated at 10:00 AM by removing the dams from the maternity cage and placing the rats in other cages. Then, the litters were removed from their home cages, weighed, and placed in the other cage during the separation.

The pups' cages contained 3 cm of fresh shavings and were placed on a heating pad set to

maintain 37 °C. At the end of the separation period, the pups were replaced in the housing cage, and the dam was transferred back to their home cage.

Another group that is mostly considered in MS as a control group is the AFR group. This group was manipulated once a week only when the home cage was changed. On day 23, the pups were weaned from their mothers and housed in groups of three to four until adolescent time.

Although both male and female pups were involved in the MS paradigm, only male rats were exposed to the following experimental procedures. In adolescent time (PND 28-34), they were assigned either to the CPP experiment and Morris water maze (MWM) test or MWM alone (Figure 1).



**Figure 1.** Treatment schedule

MS: Maternal separation; AFR: Animal facility rearing; PND: Postnatal day

**Drug:** (-)-Nicotine hydrochloride tartrate (Sigma-Aldrich; St. Louis, Missouri, USA) was dissolved in saline (0.9% NaCl) and adjusted to a pH of 7.2. Both nicotine and saline were administered subcutaneously (SC) in a volume of 1 ml/kg. The dose level of nicotine was chosen based up on previous studies supporting nicotine CPP in adolescent male rats.<sup>14,15</sup>

**CPP protocol:** Place preference conditioning was conducted as previously reported.<sup>16</sup> Briefly, two large conditioning portions A and B (40\_30\_30 cm<sup>3</sup>) were linked by a communicating tunnel (portion C: 40\_15\_30 cm<sup>3</sup>). The conditioning portions (A and B) were differentiated by their floor type and colors.

Portion A had white wood walls with 2 cm wide black horizontal stripes and a textured floor. Whereas the other portion (B) had black wood walls with 2 cm wide white vertical stripes and a smooth floor. Portion C was painted red and had a removable wooden partition that separated it from the other compartments.

The CPP procedure required three phases in 5 consecutive days: pre-test (one session),

conditioning (six sessions in 3 days), and post-test (one session). The adolescent rat pups were conditioned starting at PND 28-30 and tested on PND 32-34.

During the pre-test (day 1, PND 28-30), the removable partition was lifted and the rats could move freely from side to side in the place preference chambers for 15 min. The number of seconds spent on each compartment was calculated to determine the preferred and non-preferred chambers.

The conditioning phase started 1 day after the pre-test session. Six conditioning sessions (three saline and three nicotine), each lasting for a period of 30 min separated by 4-h interval, were conducted from day 2 to day 4 of the CPP procedure.

The rats were injected SC with either saline (1 ml/kg) or nicotine (0.6 mg/kg) and confined to one side for 30 min. half of the rats in each group received injections before exposure to the preferred portion and the other half received injections before exposure to the non-preferred portion.

During the post-test (day 5, PND 32-34), the rats received no injections and were placed in the CPP chamber for 15 min. Movement within each portion (partition in a raised position) was recorded. The change of preference was estimated as the difference (in seconds) between the periods of time spent in the drug-paired portion on the post-test and pre-test days.

**MWM test:** The MWM test was performed to evaluate the effect of MS and nicotine on spatial learning and memory using the method that was previously described by Hajali et al.<sup>17</sup>

Each rat received three blocks of training with an inter-block period of 30 min. During training, the rat was gently placed in a different quadrant of the tank and was allowed to swim to the hidden escape platform in 60 s. The position of the platform remained constant throughout the whole training period.

After finding the platform, each rat was allowed to remain for 20-30 s for orientation and returned afterwards to rest for 20-30 s in a heated cage until the next trial. The rats not able to find the platform within the time limit were placed on the platform for 10 s to associate spatial cues of the room. The time spent (escape latency) and distance traveled (escape path length) to find the platform were recorded in each trial.

Two hour after training, the probe trial was

performed in which the platform was removed and each rat was allowed to swim for 60 s. Escape latency, distance moved, velocity, and time spent in target quadrant were calculated for each rat to measure spatial memory retention.

After the probe trial, the animals were tested for their ability to find a visible platform to reveal any possibility of MS and nicotine interfering with sensory-motor coordination or motivation.

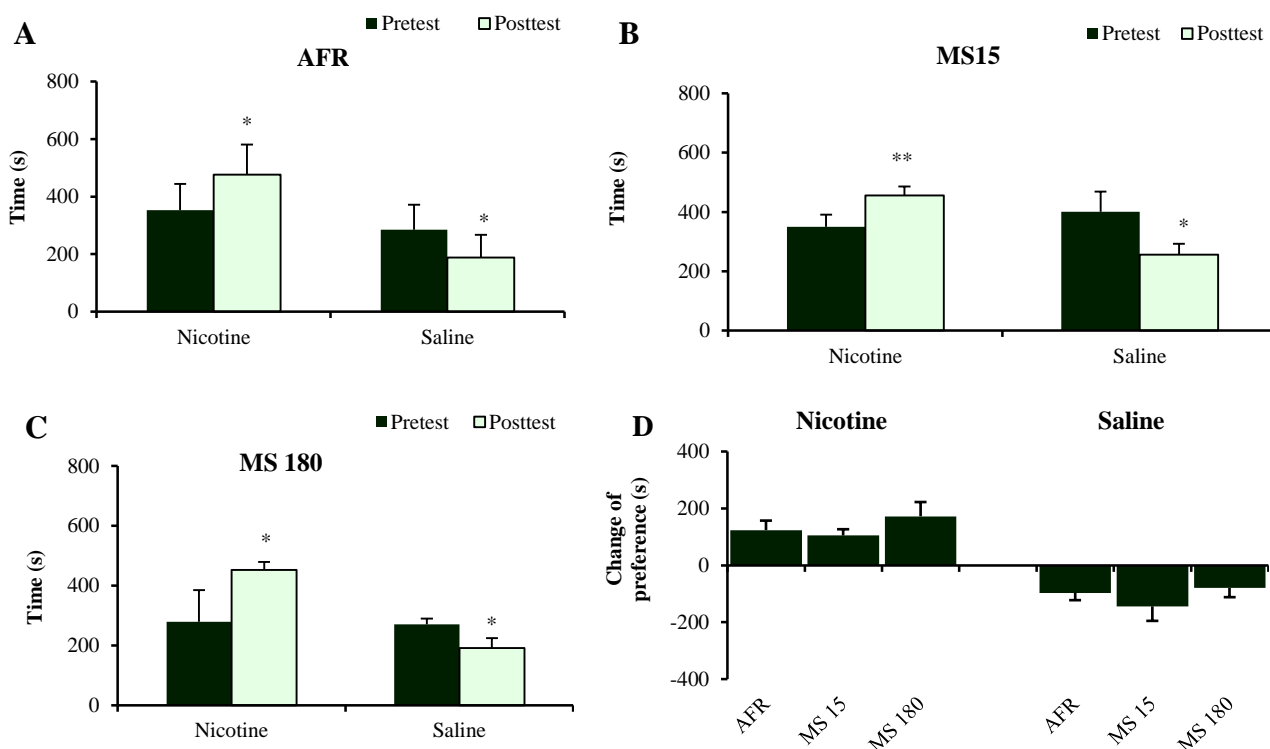
All statistical analyses were done using SPSS software (version 16, SPSS Inc., Chicago, IL, USA). Pre- and post-experimental data (nicotine, saline) were analyzed by paired-sample t-test. The time spent and distance traveled to find the hidden platform during the acquisition phase of MWM training were analyzed with two-way repeated measures analysis of variance (ANOVA) to determine the differences of the learning rates of the groups (with group and block as the between and within factors, respectively). One-way ANOVA followed by Tukey's post hoc multiple comparison test were performed to analyze group

differences for the data collected in the MWM probe trials, swim speed, and change of preference in CPP trial (difference between pre-test and post-test). The data were expressed as mean values  $\pm$  standard error of measurement (SEM) of eight animals per group;  $P < 0.05$  was considered significant.

## Results

**Place conditioning:** In our study, nicotine at the dose of 0.6 mg/kg SC induced significant place-preference in adolescent male rats in all groups. All three groups demonstrated a preference for nicotine-paired compartment in the post-test day (AFR:  $P = 0.014$ ; MS15:  $P = 0.005$ ; MS180:  $P = 0.014$ ) (Figure 2, A-C).

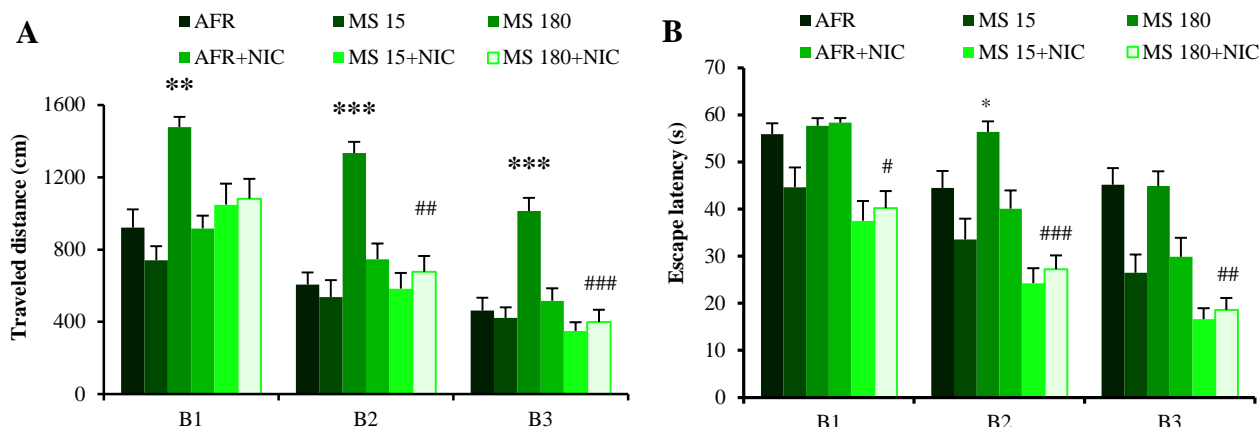
The analysis showed a non-significant effect of the treatment on the CPP score ( $F_{2,16} = 0.809$ ,  $P = 0.460$ ). Therefore, exposure to MS in PND 1-14 for 15 or 180 min/day did not affect nicotine-induced place-preference (change of preference) in comparison with the AFR group (Figure 2, D).



**Figure 2.** Pre- and post-test values of the total time spent on the drug-paired chamber during the pre- and post-test sessions (15 min) in animal facility rearing (AFR), maternal separation-15 (MS15), and MS180 groups

The animals, which received nicotine (0.6 mg/kg, SC) twice per day, during six sessions, exhibited preference for drug-paired compartment. Paired-sample t-tests indicated the significant effect of conditioning trial (A-C). The change of preference was assessed as the difference between the time spent on the post- and pre-conditioning days (one-way ANOVA followed by Tukey test) (D) Data are expressed as mean  $\pm$  SEM of 6-8 rats per group.

\* $P \leq 0.050$  and \*\* $P \leq 0.010$



**Figure 3.** Average traveled distance (cm) and escape latency (s) to find the hidden platform across 3 blocks of acquisition training in the MWM test (A and B)

The swimming distance of the MS180 group significantly increased compared to those of the AFR and MS15 groups. The mean escape latency in block 2 also increased in the MS180 group in comparison with that of the MS15 rats (A, B). \* $P \leq 0.050$ , \*\* $P \leq 0.010$  and \*\*\* $P \leq 0.001$ , indicating the differences with the AFR and MS180 groups. However, impairment in spatial learning caused by prolonged period of separation in the MS180 rats was reversed by nicotine administration (A, B). # $P \leq 0.050$ , ## $P \leq 0.010$  and ### $P \leq 0.001$ , indicating the differences with the MS180 + nicotine group (Two-way analysis of variance along with repeated measures). Data are expressed as mean + SEM (6-8 rats/group).

AFR: Animal facility rearing; MS: Maternal separation; NIC: Nicotine

**Spatial learning:** During the learning phase, animals in all groups learned to find the hidden platform as displayed by the decrement in their swimming distance and escape latency across subsequent blocks of training (Figure 3, A and B).

Repeated measures of variance analysis revealed that the swimming distance of the MS180 group significantly increased in 3 blocks of training compared to those of the AFR and MS15 groups (B1:  $P = 0.009$ ,  $P < 0.001$ ; B2:  $P < 0.001$ ,  $P < 0.001$ ; and B3:  $P < 0.001$ ,  $P < 0.001$ , respectively).

The mean escape latency in block 2 also increased in the MS180 group in comparison with the MS15 rats ( $P = 0.024$ ).

The amount of distance traveled in the AFR compared to AFR + nicotine group and in MS15 compared to the MS15 + nicotine group was not significant in 3 blocks (Figures 3, A and B). However, administration of 0.6 mg/kg nicotine in

3 sessions of the CPP trial modified the ability of the MS180 animals to find the hidden platform. This was demonstrated by the significant decrement in the swimming distance in blocks 2 and 3, ( $P = 0.002$  and  $P < 0.001$ ), respectively; Figure 3, A) and a reduction in the escape latencies in 3 blocks of training ( $P = 0.013$ ,  $P = 0.001$  and  $P = 0.008$ ) (Figure 3, B) compared to those in the nicotine group in the MWM test.

These results showed that MS in PND 1-14 for 180 min/day impaired acquisition and performance of the MWM task and that treatment with nicotine attenuated MS-induced learning deficit in the MS180 group.

On the other hand, MS status or nicotine treatment did not affect the swimming speed and visible platform phase in MWM, revealing that visual and motor functions did not change among the groups ( $P = 0.170$  and  $P = 0.810$ ) (Table 1).

**Table 1.** Comparison of swimming speed and latency to escape onto the visible platform in Morris water maze (MWM) test among groups (One-way ANOVA followed by Tukey's test)

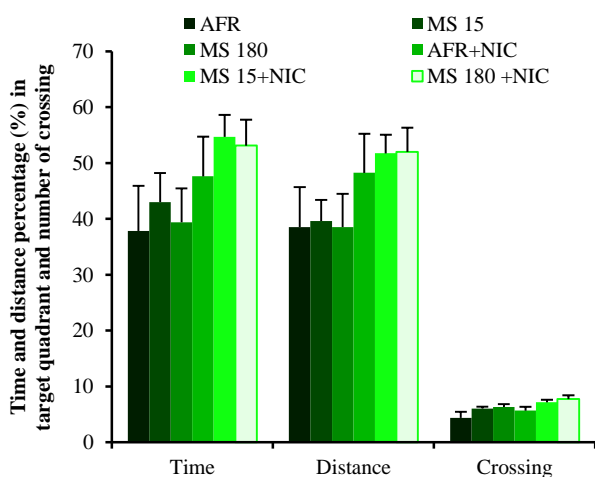
Groups (8 rats/group)	Swimming speed (cm/s)	Escape latency to visible platform (s)
	Mean + SEM	Mean + SEM
AFR	28.37 ± 2.42	20.85 ± 1.95
MS15	23.89 ± 0.60	19.14 ± 4.90
MS180	26.19 ± 0.49	23.71 ± 2.98
AFR + NIC	27.00 ± 0.69	22.28 ± 3.76
MS15 + NIC	24.48 ± 0.68	18.14 ± 3.79
MS180 + NIC	24.21 ± 0.72	19.42 ± 2.99

SEM: Standard error of measurement; AFR: Animal facility rearing; MS: Maternal separation; NIC: Nicotine

**Spatial short term memory:** The results of the spatial memory in probe trial are shown in figure 4. The mean percentage (%) for time and distance along with the number of crossing in the target quadrant, which were accomplished 2 h after acquisition, have been considered as the short term spatial memory retention.

One-way ANOVA and Tukey's post hoc analysis indicated that swimming time ( $P = 0.230$ ), distance ( $P = 0.210$ ), and number of crossing ( $P = 0.090$ ) in the target quadrant were not different among the AFR, MS15 and MS180 groups.

Similar to the MS condition, memory performance was also not influenced by administration of 0.6 mg/kg nicotine in 3 sessions of the CPP task. There were no significant differences in the time spent, distance, and number of crossing in the target quadrant during the probe trial among the treatment groups (One-way ANOVA followed by Tukey's test) (Figure 4).



**Figure 4.** Effects of MS on spatial short-term memory in the probe trial, 2h after block 3 of training in adolescent male rats

There were no significant differences in the swim time, distance, and number of target crossings during probe trial among the treatment groups (One-way ANOVA followed by Tukey's test). Data are expressed as mean + SEM (6-8 rats/group).

AFR: Animal facility rearing; MS: Maternal separation; NIC: Nicotine

## Discussion

The main aim of this study was to determine the effect of MS on the vulnerability to nicotine addiction in adolescent male rats. We investigated the consequences of MS in PND 1-14 for 3h on a daily basis, by evaluation of nicotine rewarding effects in the CPP paradigm during adolescent

period. Nicotine (0.6 mg/kg) led to a significant preference for the nicotine-paired compartment in rats subjected to short (15 min) and prolonged (180 min) periods of separation as well as in the AFR control groups.

These findings are in agreement with previous reports on nicotine-CPP in which adolescent rats generally exhibited a preference for 0.6 mg/kg nicotine.<sup>14,15</sup>

The MS procedure used in the present experiments did not affect preference for a nicotine-paired compartment in the adolescent rats. Some studies have shown that a large percentage of nicotine addiction and other substances abuse begins during adolescence and continues through adulthood.<sup>18</sup> More studies have investigated the consequence of MS and its relationship to later drug abuse especially in adult animals.<sup>8</sup> However little is known about the adolescence as a critical phase in development and increase in risk-taking exploration, following exposure to early adverse life experiences.<sup>9</sup>

Previous studies have confirmed that MS is a risk factor for morphine dependency and cocaine and methamphetamine self-administration in adult male rats and alcohol consumption during adolescence and adulthood.<sup>8</sup> In contrast, adolescent rats have been reported to have a reduced sensitivity to amphetamine induced place preference.<sup>19</sup> Another study found that adolescent rats were less sensitive to acute effects of cocaine compared with adult rats.<sup>20</sup>

The discrimination between findings could be explained by differences in the rat strain, age and sex of subjects, separation procedures, and stages of development during which the animals were tested.<sup>21,22</sup>

With regard to the long-term effects of neonatal MS, another major finding in our investigation was that adolescent rats exposed to the prolonged (180 min) period of separation in PND 1-14 displayed performance deficits in spatial learning which was assessed in the MWM task during adolescence. The traveled distance and escape latency gradually decreased in the three groups during the 3 training blocks in the MWM test, and the MS180 group showed severe cognitive deficits in the acquisition of all the three blocks compared to the AFR and MS15 groups.

It has been previously shown that a single 24-h MS on PND 3 impaired spatial learning ability in

the MWM task at 3 and 12 months of age in male rats.<sup>23</sup> In another study, the severity of cognitive deficits associated with early maternal deprivation was demonstrated by reduction in prepulse inhibition (PPI), impaired spatial learning ability and a tendency for impaired spatial working memory in adult rats.<sup>24</sup>

It has been suggested that inhibiting neurogenesis in the dentate gyrus, neurochemical changes in the hippocampus, hippocampal brain-derived neurotrophic factor levels, and NMDA receptor subunits may potentially lead to cognitive deficits in maternally separated rats.<sup>25-27</sup> In this respect, further studies are required to identify neurobehavioral and neuroendocrine mechanisms correlated with the cognitive deficits in male maternally separated rats, especially during adolescence.

The results of our study showed that administration of nicotine within 3 days markedly improved the learning impairment induced by MS occurred in these rats with age. A series of experimental studies conducted on rats have also indicated that administration of nicotine or nicotinic agonists, either acutely or chronically, improves working memory function, facilitates retention of avoidance training, and enhances MWM performance in rats.<sup>28-31</sup>

Hippocampus, with high concentrations of nicotinic acetylcholine receptors, is an important

region involved in mediating the cognitive enhancing effects of nicotine. It has been suggested that nicotine can enhance hippocampal synaptic plasticity and promote induction of long-term potentiation in dentate gyrus by activation of nicotinic acetylcholine receptors.<sup>32,33</sup>

The molecular mechanisms by which nicotine is able to produce its cognitive effects in maternally separated rats have not been completely comprehended and need further investigation.

### Conclusion

In conclusion, responses of the adolescent male rats to nicotine consumption may not be altered by the MS procedures in this study. However, prolonged (180 min) periods of separation in PND 1-14 had adverse effects on learning ability in the adolescent male rats. On the other hand, nicotine administration may contribute to the improvement of learning function and cognitive deficit following early life stress.

### Conflict of Interests

The Authors have no conflict of interest.

### Acknowledgements

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# اثرات جدایی از مادر بر القای ترجیح مکان شرطی توسط نیکوتین و عملکرد حافظه و یادگیری فضایی متعاقب آن در موش‌های صحرایی نوجوان نر

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## مقاله پژوهشی

### چکیده

**مقدمه:** اختلال در مراقبت مادری در دوره ابتدایی پس از تولد، با افزایش خطر سوء مصرف مواد در بزرگسالی ارتباط دارد. با این وجود، اثر جدایی از مادر به عنوان مدلی از استرس دوران ابتدایی پس از تولد، بر وابستگی به نیکوتین در دوران نوجوانی مشخص نیست. هدف از انجام مطالعه حاضر، بررسی تأثیر جدایی از مادر بر القای ترجیح مکان شرطی توسط نیکوتین در موش‌های صحرایی نر در دوران نوجوانی بود. علاوه بر این، اثر نیکوتین بر اختلال یادگیری و حافظه فضایی ایجاد شده به دنبال تجربه جدایی از مادر در موش‌های صحرایی نر مورد ارزیابی قرار گرفت.

**روش‌ها:** نوزادان موش‌های صحرایی طی دو هفته اول پس از تولد تحت فرایند جدایی از مادر به صورت روزانه ۱۵ دقیقه یا ۱۸۰ دقیقه قرار گرفتند. از موش‌های صحرایی که تحت شرایط طبیعی حیوان خانگی نگهداری می‌شدند، جهت گروه شاهد استفاده شد. در روز ۲۸ تا ۳۴ پس از تولد، القای مکان شرطی با استفاده از نیکوتین (۰/۶ میلی‌گرم بر کیلوگرم به صورت زیرجلدی) در روشی پنج روزه در مورد همه گروه‌ها صورت گرفت و در مرحله بعدی حافظه و یادگیری فضایی با استفاده از آزمون Morris water maze (MWM) سنجیده شد.

**یافته‌ها:** فرایند جدایی از مادر اثری بر تغییر انگیزش موش‌های صحرایی نر برای دریافت نیکوتین در آزمون القای مکان شرطی نداشت، اما باعث اختلال در یادگیری فضایی در موش‌های صحرایی در دوران نوجوانی شد. از سوی دیگر، دریافت نیکوتین اختلال یادگیری ذکر شده را تعدیل نمود.

**نتیجه‌گیری:** هرچند جدایی از مادر اثری بر افزایش حساسیت موش‌های صحرایی نر نسبت به خواص پاداشی نیکوتین در دوران نوجوانی نداشت، اما اثرات مخرب جدایی از مادر بر یادگیری فضایی با استفاده از نیکوتین تحت تأثیر قرار گرفت.

**واژگان کلیدی:** جدایی، نیکوتین، یادگیری فضایی، حافظه فضایی، موش صحرایی

**ارجاع:** دلاوری فاطمه، شیبانی وحید، اسماعیل پور خدیجه، اسماعیلی ماهانی سعید، نخعی نوذر. اثرات جدایی از مادر بر القای ترجیح مکان شرطی توسط نیکوتین و عملکرد حافظه و یادگیری فضایی متعاقب آن در موش‌های صحرایی نوجوان نر. مجله اعتیاد و سلامت ۱۳۹۵؛ ۸ (۴): ۲۶۹-۲۶۱.

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