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# HARMALINE-INDUCED AMNESIA: POSSIBLE ROLE OF THE AMYGDALA DOPAMINERGIC SYSTEM

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**Abstract—In this study, we examined the effect of bilateral intra-basolateral amygdala (intra-BLA) microinjections of dopamine receptor agents on amnesia induced by a β-carboline alkaloid, harmaline in mice. We used a step-down method to assess memory and then, hole-board method to assess exploratory behaviors. The results showed that pre-training intra-BLA injections of dopamine D1 receptor antagonist and agonist (SCH23390 (0.5 μg/mouse) and SKF38393 (0.5 μg/mouse), respectively) impaired memory acquisition. In contrast, pre-training intra-BLA injections of dopamine D2 receptor antagonist and agonist (sulpiride and quinpirole, respectively) have no significant effect on memory acquisition. Pre-training intraperitoneal (i.p.) injection of harmaline (1 mg/kg) decreased memory acquisition. However, co-administration of SCH 23390 (0.01 μg/mouse) with different doses of harmaline did not alter amnesia. Conversely, pre-training intra-BLA injection of SKF38393 (0.1 μg/mouse), sulpiride (0.25 μg/mouse) or quinpirole (0.1 μg/mouse) reversed harmaline (1 mg/kg, i.p.)-induced amnesia. Furthermore, all above doses of drugs had no effect on locomotor activity. In conclusion, the dopamine D1 and D2 receptors of the BLA may be involved in the impairment of memory acquisition induced by harmaline.**
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**Key words: harmaline, dopamine, step-down, BLA, memory.**

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*Abbreviations:* ANOVA, analysis of variance; i.p., intra-peritoneal; intra-BLA, intra-basolateral amygdala; MAO-A, monoamine oxidase A.

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## INTRODUCTION

The amygdala is a prominent limbic structure (Fudge and Emiliano, 2003), which receives dense dopaminergic afferents from the ventral tegmental area (Rezayof et al., 2002). The amygdala contains a low to high density of the dopamine D1 and D2 receptors distributed in a topographically differentiated way (Takahashi et al., 2010; Zarrindast et al., 2011; Perez de la Mora et al., 2012). The dopaminergic system of the amygdala has been implicated in the learning process (Fazli-Tabaeia et al., 2008), sensory-driven affective processing and learned aversive associations (Zarrindast et al., 2008c). Five different dopamine receptors have been recognized, which are the G protein-coupled and are categorized as belonging to one of the two classes nominated as the D1-like (D1 and D5) or D2-like (D2, D3, and D4) receptors (Vallone et al., 2000; Rezayof et al., 2007; Gonzalez-Burgos and Feria-Velasco, 2008; Hernandez et al., 2014). These two receptors exert their biological effects via coupling to and activating diverse G-protein complexes. The dopamine D1 receptor interacts with the Gs complex to activate adenylcyclase, but D2 interacts with the Gi to inhibit cyclic adenosine monophosphate production (Bressan and Crippa, 2005; Marsden, 2006; Zarrindast et al., 2006; Ferreira et al., 2011). Several enzymes are responsible for the metabolism of dopamine, including monoamine oxidase A (MAO-A) and catechol-O-methyltransferase (COMT) (Serretti and Artioli, 2004; Bressan and Crippa, 2005).

Harmaline (7 methoxy 3,4-dihydro-b-carboline), an alkaloid derived from seeds of plant Peganum harmala (Frostholm et al., 2000; Jimenez et al., 2008; Rook et al., 2010), is a MAO inhibitor (Frostholm et al., 2000; Bonnet et al., 2008; Jimenez et al., 2008; Nenaah, 2010; Nasehi et al., 2012). Several investigations indicated a wide spectrum of therapeutic activities for β-carboline alkaloids such as anticancerous property (Nenaah, 2010), neuroregulatory effect (Munoz et al., 2000; Splettstoesser et al., 2005; Moura et al., 2006), antibiotic properties (Martin et al., 1997; Hamsa and Kuttan, 2010; Yang et al., 2011), antidepressant-like effect (Herraiz and Chaparro, 2005), anxiety, learning processes (Venault and Chapouthier, 2007), and euphoria (Rommelspacher et al., 1980). Interestingly, β-carboline alkaloids may exist in biological tissues, including the blood plasma, heart, kidney, liver and brain tissue (Ruiz-Durantez et al., 2001; Splettstoesser et al., 2005; Moura et al., 2006; Rook et al., 2010; Nasehi et al., 2012). β-carbolines have a mixed pharmacology and individual compounds have been shown to bind to a

variety of different targets including the MAO-A and MAO-B, benzodiazepine, imidazoline, dopamine and serotonin receptors (Herraiz and Chaparro, 2005; Moura et al., 2006; Talhout et al., 2007; Nasehi et al., 2010). β-carboline alkaloids increase the extracellular norepinephrine, dopamine and serotonin levels in several brain areas by inhibition of monoamine reuptake systems (Venault and Chapouthier, 2007; Nasehi et al., 2010, 2012). Some evidence demonstrated that harmaline could influence the dopaminergic transmission (Kadivar et al., 2014; Naseri et al., 2014), which may be done by inhibition of the MAO-A or MAO-B (Herraiz and Chaparro, 2005; Touiki et al., 2005; Talhout et al., 2007; Yang et al., 2011). Given that the amygdala function is importantly modulated by dopamine (Zarrindast et al., 2008c; Rezayof et al., 2009), and considering the interaction between dopamine and harmaline (Kadivar et al., 2014; Naseri et al., 2014), the present study has examined the role of dopamine receptors and harmaline in memory acquisition and locomotor activity in the step-down passive avoidance and open field test.

## EXPERIMENTAL PROCEDURES

### Animals

Adult male NMRI mice weighing 25–30 g obtained from the Institute of Cognitive Science (Tehran, Iran) were used. They were housed ten per cage, in a room under a 12-h light:12-h dark cycle (lights on 07:00 h) and controlled temperature (23 ± 1 °C) with free access to food and water except during the limited times of experiments. Animals were handled about 3 min each day prior to behavioral testing. Behavioral tests were performed during the light phase of the cycle between 8:00 and 12:00 h and each mouse was tested only once. All procedures in the current investigation were approved by the Ethics Committee of the Faculty of Science of the University of Tehran which corresponds to the national guidelines for animal care and use.

### Stereotaxic surgery

Animals were anesthetized with intraperitoneal administration of ketamine/xylazine mixture (50 mg/kg and5 mg/kg, respectively) and positioned in a stereotaxic apparatus (Stoelting Co, Illinois, USA). Afterward, the skin was slit and the skull was cleaned. Following, stainless steel guide cannulae (22 gauge, 0.7 mm diameter) were placed bilaterally 1 mm above the intended site of injection according to the atlas of Paxinos and Franklin (Paxinos and Franklin, 2001). Stereotaxic coordinates for the BLA were: −0.8 mm caudal, ±2.7 mm mediolateral, and 3.9 mm dorsoventral to the bregma. The cannulae were anchored to the skull with a jeweler's screw and dental cement. After the surgery, two stainless steel stylets (27-gauge) were inserted into the guide cannulae to conserve them free of debris. All mice were allowed 5–7 days to recover from the surgery and get cleared from effects of the anesthetic drugs.

### Memory testing and apparatus

The inhibitory avoidance apparatus was made of a wooden box ($30 \times 30 \times 40\ cm^3$) with a floor which consisted of parallel caliber stainless steel bars (0.3 cm in diameter, spaced 1 cm apart). A wooden platform ($4 \times 4 \times 4\ cm^3$) was placed in the center of the grid floor. Electric shocks (1 Hz, 0.5 s and 50 VDC) were conveyed to the grid floor by an isolated stimulator (Borj Sanat Co, Tehran, Iran).

For testing, animals were trained on a single-trial step-down passive avoidance task. In the training session, each animal was gently located on the wooden platform. Once the mouse stepped down from the platform and put all four paws on the grid floor, intermittent electric shocks were delivered continuously for 15 s. The training procedure was carried out among 8:00 a.m. and 12:00 p.m. Retention test session was carried out twenty-four hours after the training session and was procedurally similar to the training, except that no shock existed. The step-down latency was measured as memory retention. An upper cut-off time of 300 s was set. The retention test was also carried out between 8:00 a.m. and 12: p.m.

### Measurement of locomotor activity

The locomotion apparatus (Borj Sanat Co, Tehran, Iran) was made of a clear perspex container box (30 cm × 30 cm × 40 cm high). This apparatus has a gray perspex panel (30 cm × 30 cm × 2.2 cm thick) with 16 photocells which divided the box to 16 equal-sized squares. Locomotor activity was measured as the number of crossings from one square to another during 300 s.

### Drugs

The drugs used in the present study were ketamine and xylazine (Alfasan Chemical Co, Woerden, Holland) for animal anesthesia. Other drugs which were supplied by Sigma, St Louis, CA, USA were: harmaline (1-methyl-7-methoxy-3,4-dihydro-bcarboline), SKF38393 (1-phenyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride), SCH23390 (R(+)-7-chloro-8-hydroxyl-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride), quinpirole and sulpiride. The compounds were tested at doses: harmaline 0.25, 0.5 and 1 mg/kg; SCH23390, 0.01, 0.1 and 0.5 μg/mouse; SKF38393, 0.1, 0.25 and 0.5 μg/mouse; sulpiride, 0.125, 0.25 and 0.5 μg/mouse; and quinpirole, 0.1, 0.25 and 0.5 μg/mouse. Harmaline was dissolved in the sterile saline and the compound was stirred for 1 h previously obtaining the final solution. Other drugs were dissolved in the physiological saline, just before the experiments, except for sulpiride which was dissolved in one drop of glacial acetic acid with a Hamilton micro-syringe and made up to a volume of 5 ml with sterile saline and was then diluted to the required volume. The dopaminergic drugs were administered into the BLA (intra-BLA) and harmaline was injected intra-peritoneally (i.p.). The time of infusion and doses of drugs used in the experiments

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