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# Involvement of dopamine $D_1/D_2$ receptors on harmane-induced amnesia in the step-down passive avoidance test

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ABSTRACT

Ingestion of harmane and other alkaloids derived from plant *Peganum harmala* has been shown to elicit profound behavioural and toxic effects in humans, including hallucinations, excitation, feelings of elation, and euphoria. These alkaloids in the high doses can cause a toxic syndrome characterized by tremors and convulsions. Harmane has also been shown to act on a variety of receptor systems in the mammalian brain, including those for serotonin, dopamine and benzodiazepines. In animals, it has been reported to affect short and long term memory. In the present study, effects of dopamine $D_1$ and $D_2$ receptor antagonists on the harmane (HA)-induced amnesia and exploratory behaviors were examined in mice. One-trial step-down and hole-board paradigms were used for the assessment of memory retention and exploratory behaviors in adult male NMRI mice respectively. Intraperitoneal (i.p.) administration of HA (5 and 10 mg/kg) immediately after training decreased memory consolidation, while had no effect on anxiety-like behavior. Memory retrieval was not altered by 15- or 30 min pre-testing administration of the $D_1$ (SCH23390, 0.025, 0.05 and 0.1 mg/kg) or $D_2$ (sulpiride 12.5, 25 and 50 mg/kg) receptor antagonists, respectively. In contrast, SCH23390 (0.05 and 0.1 mg/kg) or sulpiride (25 and 50 mg/kg) pre-test administration fully reversed HA-induced impairment of memory consolidation. Finally, neither $D_1$ nor $D_2$ receptor blockade affected exploratory behaviors in the hole-board paradigm. Altogether, these findings strongly suggest an involvement of $D_1$ and $D_2$ receptors modulation in the HA-induced impairment of memory consolidation.



## 1. Introduction

A number of tremorogenic β-carboline alkaloids such as harmane (HA; 1-methyl-β-carboline), 1-methyl-7-methoxy-3, 4-dihydro-β-carboline (harmaline) and 9H-pyrido [3, 4-β] indole (norharmane) are naturally present in the human food chain. They have been found in common plant-derived foodstuffs (wheat, rice, corn, barley, soybeans, rye, grapes, mushrooms, and vinegar), plant-derived beverages (wine, beer, whisky, brandy, and sake), and plant-derived inhaled substances (tobacco)(Adachi et al., 1991). The β-carbolines HA, norharmane and harmine exist in the blood plasma, heart, kidney, liver and also in brain tissue (Hudson et al., 1999; May et al., 1994; Rommelspacher et al., 1980). Since, high plasma levels of these compounds have been found in heavy smokers (Spijkerman et al., 2002), alcoholics (Rommelspacher et al., 1991b), heroin-dependent humans (Stohler et al., 1996), patients with essential tremor (Louis et al., 2002) or Parkinson's disease (Kuhn et al., 1996), they are assumed to have a crucial role in the pathophysiology of various disorders of the CNS. Condensation reaction between an indoleamine and acetaldehyde forms the molecule in peripheral and brain tissue (Susilo et al., 1987). On the other hand, there is evidence showing that formation of β-carbonile can be achieved by enzymatic processes, because it only occurs in the presence of mammalian tissue. In particular, experiments performed in vitro under pseudo-physiological conditions with [3H]tryptamine and pyruvic acid failed to result in β-carboline formation, indicating that an enzymatic process was involved (Rommelspacher et al., 1991a). The β-carbolines have a mixed pharmacology and individual compounds have been shown to bind to a variety of different targets including monoamine oxidase A

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and B ($MAO_A$ and $MAO_B$), benzodiazepine, imidazoline, dopamine and 5-hydroxytryptamine (5-HT) receptors (Glennon et al., 2000; Pahkla et al., 1997; Rommelspacher et al., 1980; Taylor et al., 1984). B-carboline alkaloids increase the extracellular norepinephrine, dopamine and 5-HT levels in several brain regions via inhibition of monoamine reuptake systems (Baum et al., 1996; Kleven and Woolverton, 1993; Komulainen et al., 1980; Tella, 1995). These compounds also increase the levels of monoamines after monoamine oxidase (MAO) $_A$ or $_B$ inhibition (Adell et al., 1996; Fuller et al., 1986; Rommelspacher et al., 1994).

Moreover, dopamine exerts its action by binding to specific membrane receptors (Gingrich and Caron, 1993). The dopamine receptors were classified as $D_1$-like and $D_2$-like based on sequence homology and pharmacology (Civelli et al., 1993; Missale et al., 1998; Seeman and Van Tol, 1993). A large number of different paradigms have been used to demonstrate that dopamine receptors play a critical role in the modulation of neuronal activities that are related to different forms of learning and memory (see (Jay, 2003) for a review). Adriani reported that dopamine receptors are also able to alter the capability to learn and store information (Adriani et al., 1998). A method based on the measurement of step-down latency in passive avoidance has been developed for the study of learning and memory in mice (Kameyama et al., 1986).

On the other hands, the research in anxiety is focused on serotonergic, GABAergic and adrenergic neurotransmitter systems but also dopamine has been discussed to be involved in anxiety. In conclusion, because of β-carboline presence in the food chain and that these alkaloids have a wide spectrum of pharmacological actions and immunomodulatory effects, in the present study, the effects of HA on memory consolidation/exploratory behaviors and involvement of $D_1/D_2$ receptors on these behaviors in the step-down passive avoidance and hole-board test in mice have been investigated.

## 2. Materials and methods

### 2.1. Animals

Male albino NMRI mice weighing 25–30 g were used. Animals were kept in an animal house with a 12/12-h light–dark cycle and controlled temperature (22 ± 2 °C). Animals were housed in groups of 10 in Plexiglas cages and they had free access to food and tap water except during the limited periods of experiments. Ten animals were used in each group; each animal was used once only. Behavioural experiments were done during the light phase of the light/dark cycle. All procedures were carried out in accordance with institutional guidelines for animal care and use.

### 2.2. Memory testing and apparatus

An inhibitory avoidance apparatus consisted of a wooden box ($30 \times 30 \times 40$ $cm^3$) with a floor that consisted of parallel stainless steel rods (0.3 cm in diameter, spaced 1 cm apart). A wooden platform ($4 \times 4 \times 4$ $cm^3$) was set in the center of the grid floor. Electric shocks (1 Hz, 0.5 s and 50 V DC) were delivered to the grid floor by an isolated stimulator (Grass S44, Quincy, MA, USA).

For testing, each mouse was gently placed on the wooden platform. When the mouse stepped down from the platform and placed all its paws on the grid floor, intermittent electric shocks were delivered continuously for 15 s (Zarrindast et al., 2009; Zarrindast et al., 2008). This training procedure was carried out between 9:00 a.m. and 2:00 p.m. Twenty-four hours after training, each mouse was placed on the platform again, and the step-down latency was measured with a stop-watch as passive avoidance behavior. An upper cut-off time of 300 s was set. The retrieval test was also carried out between 9:00 a.m. and 2:00 p.m.

### 2.3. Exploratory behavior testing and apparatus

The hole-board test as a simple method for examining the response of an animal to an unfamiliar environment was first introduced by Boissier and Simon (1962). This test has been used to evaluate emotionality, anxiety and/or responses to stress in animals (Rodriguez Echandia et al., 1987). Different behaviors which can be observed and measured in this test, makes possible a comprehensive description of the animal's behavior. The hole-board apparatus (Borj Sanat Co, Tehran, Iran) consisted of gray Perspex panels (40 cm × 40 cm, 2.2 cm thick) with 16 equidistant holes 3 cm in diameter in the floor made on the basis of method used previously (Vinade et al., 2003). The board was positioned 15 cm above a table.

For anxiety testing, 5 min after memory testing, animals were placed singly in the center of the board facing away from the observer and head-dip numbers were recorded by photocells arranged below the holes over 5 min. Increase or decrease in head-dips indicated anxiolytic-like or anxiogenic-like behavior respectively. Furthermore, locomotor activity was measured by an observer unaware of the treatments measured during the testing phase. For this purpose the ground area of the hole-board were divided into four equal sized squares. Locomotion was measured as the number of locomotor activity crossings from one square to another. Other behavioural performance such as latency to the first head-dipping, rearing, grooming and defecation was recorded by the experimenter during the test, manually.

### 2.4. Drugs

The drugs used in the present study were HA (1-methyl-9H-pyridol [3,4-b]indole, C12H10N2) from Sigma (St. Louis, MO), $D_1$ receptor antagonist, SCH23390 (R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride) and $D_2$ receptor antagonist, sulpiride from Sigma (St Louis, CA, USA). The time of injection and doses of compounds used in the experiments were chosen according to published work in scientific literature (Rezayof et al., 2006; Zarrindast and Rezayof, 2004). All the compounds were tested at three doses: harmane (HA) 2.5, 5 and 10 mg/kg; SCH23390, 0.025, 0.05 and 0.1 mg/kg; sulpiride, 12.5, 25 and 50 mg/kg. HA was dissolved in sterile 0.9% NaCl solution and the compound was stirred for 1 h before obtaining the final solution; SCH23390 was dissolved in 0.9% physiological saline, just before the experiments. Sulpiride was dissolved in a minimal volume of diluted acetic acid (1 drop; 5 µl; pH: 6.3 by Hamilton micro-syringe 10 µl) and made up to a volume of 5 ml with 0.9% physiological saline and was then diluted to the required volume with saline (0.9%w/v NaCl solution).

### 2.5. Drug treatment

Ten animals were used in each experimental group. In experiments where animals received two injections, control groups received either two saline (10 ml/kg) or vehicle (10 ml/kg) injections. Moreover, control groups for HA and SCH23390 treatment in Experiments 1 and 2 received saline 0.9% physiological saline while control groups for sulpiride in the Experiment 3 received 0.9% physiological saline or vehicle (PH = 7.2; solution used for sulpiride). All drugs were injected intraperitoneally (i.p.) in a volume of 10 ml/kg. Furthermore, the timing of the pre-test drug administration was selected based on pilot and previous studies (Rezayof et al., 2006; Zarrindast and Rezayof, 2004). The protocol has been summarized in Table 1.

#### 2.5.1. Experiment 1: effects of post-training HA administration on memory consolidation and exploratory behaviors

In this experiment, four groups of animals received saline (10 ml/kg) or different doses of HA (2.5, 5 and 10 mg/kg, i.p.) immediately after training, and in the test's day all groups received saline (10 ml/

**Table 1**
Summary of experimental design.

| Figure | | First day; post-training treatment (i.p.) | | Second day; pre-test treatment (i.p.) | | | | Effect upon specific behavior | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Saline (ml/kg) | Harmane (mg/kg) | Saline (ml/kg) | Vehicle (ml/kg) | SCH23390 (mg/kg) | Sulpiride (mg/kg) | Avoidance response (panel A) | Head-dips (panel B) | Locomotor activity (panel C) |
| 1 | | 10 | 2.5–10 | 10 | – | – | – | Decrease | NO effect | NO effect |
| 2 | Left | 10 | – | 10 | – | 0.2–0.1 | – | NO effect | Decrease | Decrease |
| | Right | – | 5 | 10 | – | 0.25–0.1 | – | Increase | NO effect | Decrease |
| 3 | Left | 10 | – | 10 | 10 | – | 12.5–50 | NO effect | Decrease | Decrease |
| | Right | – | 5 | – | 10 | – | 12.5–50 | Increase | Decrease | Decrease |

kg, i.p.) 30 min before testing. The exploratory behaviors of animals were recorded by hole-board task, 5 min after memory testing.

*2.5.2. Experiment 2: effects of pre-test SCH23390 administration on memory retrieval and exploratory behaviors under the disruptive influence of HA treatment*

In this experiment, eight groups of animals were used. Four groups of animals received saline (10 /kg, i.p.) immediately after training, and they received saline (10 ml/kg, i.p.) or SCH23390 (0.025, 0.05 and 0.1 mg/kg, i.p.) 15 min before testing. The exploratory behaviors of animals were recorded by hole-board task, 5 min after memory testing. Another four groups of animals received post-training HA (1 mg/kg, i.p.), and 24 h after training, they received saline (10 ml/kg, i.p.) or SCH23390 (0.025, 0.05 and 0.1 mg/kg, i.p.) 15 min before testing. The exploratory behaviors of animals were recorded by hole-board task, 5 min after memory testing.

*2.5.3. Experiment 3: effects of pre-test sulpiride administration on memory retrieval and exploratory behaviors under the disruptive influence of HA treatment*

In this experiment, nine groups of animals were used. Five groups of animals received saline (10 ml/kg, i.p.) immediately after training, and they received saline (10 ml/kg, i.p.), vehicle (10 ml/kg, i.p.) or sulpiride (12.5, 25 and 50 mg/kg, i.p.), 30 min before testing. The exploratory behaviors of animals were recorded by hole-board task, 5 min after memory testing. Another four groups of animals received post-training HA (5 mg/kg, i.p.), and they received saline (10 ml/kg, i.p.) or sulpiride (12.5, 25 and 50 mg/kg, i.p.), 30 min before testing. The exploratory behaviors of animals were recorded by hole-board task, 5 min after memory testing.

*2.6. Statistical analysis*

Because of individual variations the data of step-down apparatus, the data obtained were analyzed by using the Kruskal–Wallis nonparametric one-way analysis of variance (ANOVA) followed by a two-tailed Mann–Whitney's *U*-test. Holmes Sequential Bonferroni Correction Test was used for the paired comparisons as appropriate. The step-down latencies for ten animals in each experimental group were expressed as median and inter-quartile ranges. On the other hands, the data obtained from hole-board apparatus are presented as the mean ± S.E.M. One-way repeated measures analysis of variance (ANOVA) followed by post hoc's test was used for the statistical evaluation. In all statistical evaluations $P<0.05$ was used as the criterion for statistical significance.

## 3. Results

*3.1. Effects of post-training HA administration on memory consolidation and exploratory behaviors*

Fig. 1A shows the effects of post-training administration of HA on step-down latency. Kruskal–Wallis ANOVA ($H(3)=127.81$, $P<0.001$) reveals post-training administration of HA (2.5, 5 and 10 mg/kg, i.p.) dose-dependently reduced the step-down latency in the one-trial passive avoidance task. Post hoc analysis by Mann–Whitney's *U*-test indicates HA (5 and 10 mg/kg) impaired memory consolidation, thus showing an amnesic effect.

In addition, Fig. 1B, C indicates the effects of HA on exploratory behaviors. One-way ANOVA reveals HA (2.5, 5 and 10 mg/kg, i.p.) did not alter the number of head-dips [$F(3, 36)=2.12$, $P>0.5$] (Fig. 1B) and locomotor activity [$F(3, 36)=0.86$, $P>0.5$] (Fig. 1C). The latency to head-dipping [$F(3, 36)=0.44$, $P>0.5$], the numbers of rearing [$F(3, 36)=0.73$, $P>0.5$], grooming [$F(3, 36)=3.14$, $P>0.5$] and defecation [$F(3, 36)=1.1$, $P>0.5$] were not changed (not shown). In conclusion, the data shows HA-induced amnesia, but did not effect on anxiety-like behaviors and locomotor activity.

*3.2. Effects of pre-test SCH23390 administration on memory retrieval and exploratory behaviors under the disruptive influence of HA treatment*

Fig. 2A (left panel) shows that administration of different doses of SCH23390 (0.025, 0.05 and 0.1 mg/kg, i.p.), 15 min before testing, had

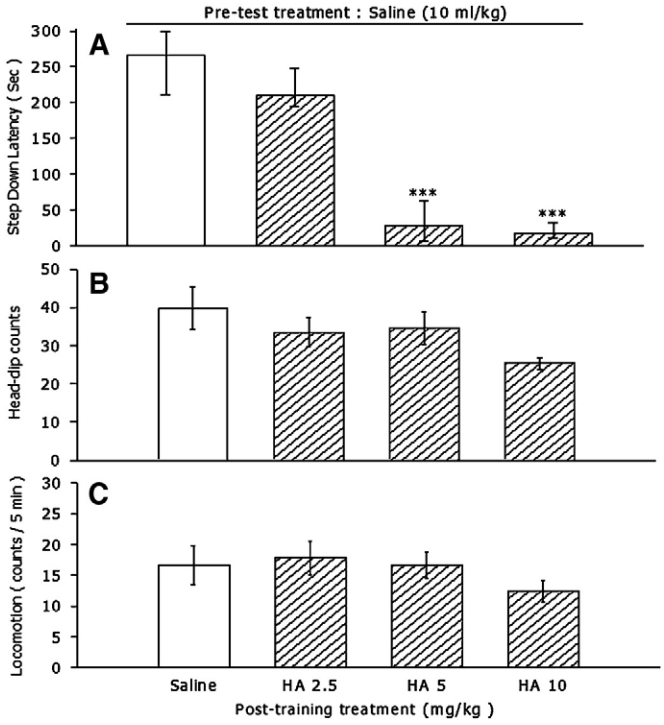


**Fig. 1.** The effects of post-training administration of HA or saline on memory consolidation and exploratory behaviors. Different doses of HA (2.5, 5 and 10 mg/kg, i.p.) or saline (10 ml/kg, i.p.) were administered immediately after training in four groups of animals. On the test day, animals received saline (10 ml/kg, i.p.) 30 min before the test. Test session step-down latencies are expressed as median and quartile for 10 animals. ***$P<0.001$, compared to post-training saline/pre-test saline. Furthermore, exploratory behaviors including number of head-dips (panel B) and locomotor activity (panel C) were examined 5 min after memory testing. Each bar is mean ± S.E.M.

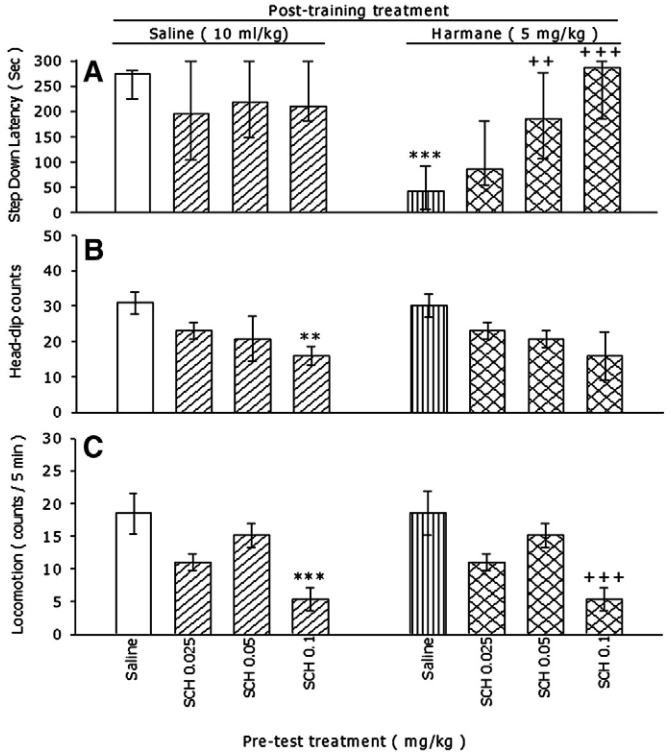


**Fig. 2.** The effects of dopamine $D_1$ receptor antagonist, SCH23390 (SCH) on memory retrieval and exploratory behaviors in the present and absence of HA. Panel A shows the effects of pre-test administration of SCH23390 (0.025, 0.05 and 0.1 mg/kg, i.p.) on animals which were trained under influence of saline (10 ml/kg, i.p.; left panel) or HA (5 ml/kg, i.p.; right panel). The effects of SCH23390 pre-test treatment have been assessed in either post-training saline/pre-testing saline (left panel) or post-training HA 5 mg/kg/pre-testing saline (right panel) groups. Test session step-down latencies are expressed as median and quartile for 10 animals. $^{**}P<0.01$, $^{***}P<0.001$, compared to post-training saline/pre-test saline. In addition, exploratory behaviors including number of head-dips (panel B, left panel; dose response of SCH23390 and right panel; effects of SCH23390 on HA response) and locomotor activity (panel D, left panel; dose response of SCH23390 and right panel; effects of SCH23390 on HA response) were examined 5 min after memory testing. The effects of SCH23390 pre-test treatment have been assessed in either post-training saline/pre-testing saline (left panels) or post-training HA 5 mg/kg/ pre-testing saline (right panels) groups. Each bar is mean ± S.E.M. $++P<0.01$ and $+++P<0.001$ when compared to HA/ saline group.

no effect on memory retrieval [Kruskal–Wallis ANOVA, $H$ (3) = 3.33, $P>0.05$]. In addition, Fig. 2B, C (left panels) indicates the effects of SCH23390 on exploratory behaviors. One-way ANOVA and post hoc analyses reveal that the SCH23390 (0.1 mg/kg, i.p.) decreased head-dips [$F$ (3, 36) = 5.11, $P<0.001$] (panel B) and locomotor activity [$F$ (3, 36) = 7.1, $P<0.001$] (panel C), but not other exploratory behaviors such as latency to head-dipping [$F$ (3, 36) = 0.4, $P>0.05$], number of rearing [$F$ (3, 36) = 0.67, $P>0.5$], number of grooming [$F$ (3, 36) = 1.01, $P>0.5$] and number of defecation [$F$ (3, 36) = 2.0, $P>0.5$]. Data for latency to head-dipping, rearing, grooming and defecation are not shown. In conclusion, the data shows SCH23390 had no effect on memory retrieval, but a higher dose of the drug (0.1 mg/kg) decreased both number of head-dip and locomotor activity.

Moreover, Fig. 2A (right panel) indicates that pre-test administration of the SCH23390 affects HA-induced amnesia [Kruskal–Wallis ANOVA, $H$ (3) = 18.06, $P<0.001$]. Mann–Whitney's $U$-test analysis reveals the antagonist doses of 0.05 and 0.1 mg/kg induced full recovery of the memory impairment caused by HA (5 mg/kg). Furthermore, Fig. 2B, C (right panel) indicates the effects of SCH23390 on exploratory behaviors-induced by HA. One-way ANOVA and post hoc analyses reveal SCH23390 (0.1 mg/kg, i.p.) decreased head-dips [$F$ (3, 36) = 3.6, $P<0.05$] (panel B) and locomotor activity [$F$ (3, 36) = 5.1, $P<0.001$] (panel C), but had no effect on other exploratory behaviors such as, latency to head-dipping [$F$ (3, 36) = 0.82, $P>0.05$], number of rearing [$F$ (3, 36) = 0.67, $P>0.5$], number of grooming [$F$ (3, 36) = 1.01, $P>0.5$] and number of defecation [$F$ (3, 36) = 2.0, $P>0.5$]. Data for latency to head-dipping, rearing, grooming and defecation are not shown. In conclusion, SCH23390 elicited full recovery of HA-induced amnesia.

### 3.3. Effects of pre-test sulpiride administration on memory retrieval and exploratory behaviors under the disruptive influence of HA treatment

Fig. 3A (left panel) shows that administration of different doses of sulpiride (12.5, 25 and 50 mg/kg, i.p.), 30 min before testing had no effect on memory retrieval [Kruskal–Wallis ANOVA, $H$ (3) = 1.87, $P>0.05$]. In addition, Fig. 3B, C (left panel) indicates that the effect of different doses of sulpiride on exploratory behaviors. One-way ANOVA and post hoc analyses reveal that sulpiride (50 mg/kg, i.p.) decreased head-dips [$F$ (4, 45) = 7.15, $P<0.001$] (panel B), locomotor activity [$F$ (4, 45) = 3.16, $P<0.05$] (panel C) but had no effect on other exploratory behaviors such as latency to head-dipping [$F$ (4, 45) = 3.8, $P>0.05$], number of rearing [$F$ (4, 45) = 0.85, $P>0.5$], number of grooming [$F$ (4, 45) = 0.15, $P>0.5$] and number of defecation [$F$ (4, 45) = 1.6, $P>0.5$]. Data for latency to head-dipping, rearing, grooming and defecation are not shown. In conclusion, the data shows that sulpiride had no effect on memory retrieval, on the other hands; a dose of the sulpiride (50 mg/kg) showed anxiogenic-like behaviors.

Furthermore, the results indicate pre-test administration of sulpiride affects HA-induced amnesia [Kruskal–Wallis ANOVA, $H$ (3) = 23.36,

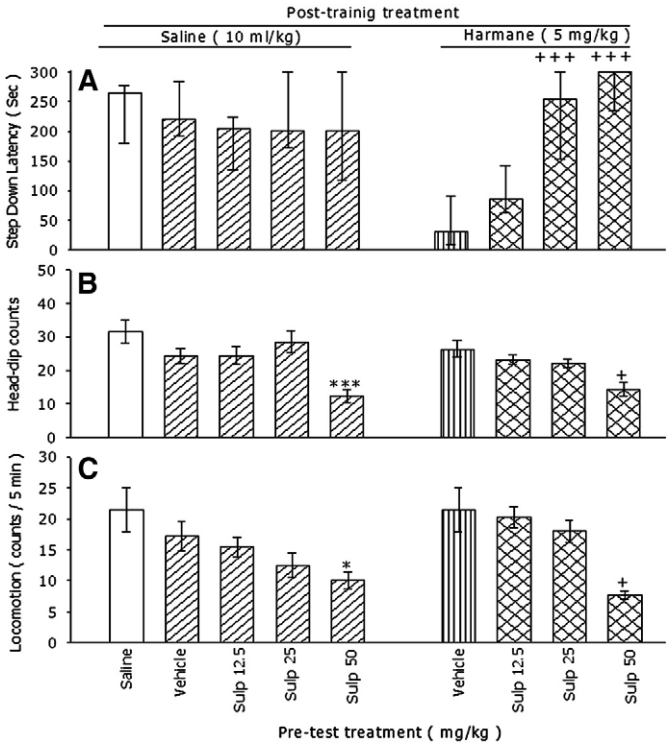


**Fig. 3.** The effects of dopamine $D_2$ receptor antagonist, sulpiride (Sulp) on memory retrieval and exploratory behaviors in present and absence of HA. Panel A shows the effects of pre-test administration of sulpiride (12.5, 25 and 50 ml/kg, i.p.) on animals which were trained by saline (10 ml/kg, i.p.; left panel) or HA (5 ml/kg, i.p.; right panel) in train's day. The effects of sulpiride pre-test treatment have been assessed in either post-training saline/ pre-testing vehicle (left panel) or post-training HA 5 mg/kg/ pre-testing vehicle (right panel) groups. Test session step-down latencies are expressed as median and quartile for 10 animals. $^{*}P<0.05$, $^{***}P<0.001$, compared to post-training saline/pre-test saline. In addition, exploratory behaviors including number of head-dips (panel B, left panel; dose response of sulpiride and right panel; effects of sulpiride on HA response) and locomotor activity (panel D, left panel; dose response of sulpiride and right panel; effects of sulpiride on HA response) were examined 5 min after memory testing. The effects of sulpiride pre-test treatment have been assessed in either post-training saline/ pre-testing vehicle (left panels) or post-training HA 5 mg/kg/pre-testing vehicle (right panels) groups. Each bar is mean ± S.E.M. $+P<0.05$ and $+++P<0.001$ when compared to HA/saline group.

$P<0.001$]. Mann–Whitney's $U$-test analysis reveals sulpiride at doses of 25 and 50 mg/kg elicited full recovery of the memory impairment by HA (Fig. 3B; right panel). On the other hand, Fig. 3B, C (right panel) indicates the effects of sulpiride on exploratory behaviors-induced by HA. One-way ANOVA and post hoc analyses reveal that sulpiride (50 mg/kg, i.p.) decreased head-dips [$F$ (3, 36) = 9.26, $P<0.001$] (panel B), locomotor activity [$F$ (3, 36) = 8.1, $P<0.001$] (panel C), increased latency to head-dipping [$F$ (3, 36) = 3.9, $P<0.05$] but had no effect on other exploratory behaviors such as number of rearing [$F$ (3, 36) = 0.70, $P>0.5$], number of grooming [$F$ (3, 36) = 0.1is, $P>0.5$] and number of defecation [$F$ (3, 36) = 2.6, $P>0.5$]. Data for latency to head-dipping, rearing, grooming and defecation are not shown. In conclusion, two doses of sulpiride (25 and 50 mg/kg, i.p.) induced full recovery of HA-induced amnesia.

## 4. Discussion

Our results indicated that post-training administration of HA, dose-dependently, impaired memory consolidation, but did not affect anxiety-like behavior and locomotor activity. Previous behavioural studies have documented a number of diverse effects for HA, such as motor depression, ataxia, catatonia, convulsions (Airaksinen et al., 1987; el Bahri and Chemli, 1991; Pranzatelli and Snodgrass, 1987; Rommelspacher et al., 1981), and reinforcement of alcohol consumption in rats (Myers and Melchior, 1977; Rommelspacher et al., 1987). There are less experiments related to the effects of harmala alkaloids on memory, however, its administration may produce hallucinations, excitation, feelings of elation, and euphoria (Rommelspacher et al., 1981). Some of investigators indicated that the alkaloid HA did not affect the formation of short and long term memories. However, the dihydro-β-carboline harmaline elicited effects on non-spatial and non-aversive memory tasks, and enhanced long term memory. Electrophysiological studies showed that harmaline may induce tremor by activating the inferior olivary nucleus and cerebellum (de Montigny and Lamarre, 1973; Lamarre and Mercier, 1971; Mehta et al., 2003). On the other hand, there are reports indicating that harmaline blocks both associative and motor learning (Du and Harvey, 1997; Welsh, 1998). Whether the inferior olive plays a role in the learning and memory is not known (Welsh and Harvey, 1998), and should be clarified.

Neurochemical and behavioural studies have elucidated the effects of β-carbolines at the cellular level. These agents may be involved in the impairment of sodium–hydrogen exchange (Anderson et al., 2003; Glennon et al., 2000) and potentiation of monoaminergic pathways through inhibition of monoamine oxidase A or B (Adell et al., 1996; Fernandez de Arriba et al., 1994; Pranzatelli and Snodgrass, 1987; Rommelspacher et al., 1994; Rommelspacher et al., 2002) (Baum et al., 1996; Ergene and Schoener, 1993) and monoamine reuptake systems (Baum et al., 1996; Kleven and Woolverton, 1993; Komulainen et al., 1980; McCormick and Tunnicliff, 1998; Tella, 1995). They may also activate monoamine receptors directly (Airaksinen et al., 1978; Davis et al., 1979; Glennon et al., 2000; Honecker et al., 1980; Kari et al., 1980; Rommelspacher et al., 1977). Moreover, excitotoxic effects of dopamine and glutamate may be protected by β-carbolines (Maher and Davis, 1996), which may indicate a protective role of β-carbolines in the pathophysiology of Parkinson's. β-carbolines were shown to reduce brain mitochondrial and synaptosomal dysfunctions due to dopamine or 6-hydroxydopamine and also the viability in PC-12 cells loss through a scavenging action on reactive oxygen species and maintenance of reduced thiols (Kim et al., 2001). Minor differences in the structural parameters of the agents lead to large differences in the affinities for their different receptors. In vivo studies demonstrated that tetrahydro-norharmane exerts high affinity for the serotonergic sites and antagonizes the effects of dopamine receptor stimulants (Airaksinen et al., 1978; Davis et al., 1979), while HA, harmine, and harmaline have high affinity for the muscarinic cholinergic and the opiate binding sites. In conclusion, the affinities of β-carbolines are highly dependent upon substitutions and ring saturation. The fully aromatic β-carbolines show more affinity for these receptors and the substitution in C7 also seems to be important in modifying its affinity for these receptors (Glennon et al., 2000).

It is also well known that dopamine plays a critical role in the modulation of neuronal activities that are related to different forms of learning and memory (see introduction). In order to get a deeper insight into the nature of HA-induced amnesia, the involvement of dopamine $D_1/D_2$ receptors on impairment of avoidance response induced by HA has been tested. Our present data indicated that the in mice trained under HA administration, pre-test administration of dopamine $D_1$ receptor antagonist, SCH23390 and dopamine $D_2$ receptor antagonist, sulpiride significantly elicited full recovery of HA-induced amnesia. Due to increase in the dopamine levels in the brain by HA and recovery of memory impairment by blockade of $D_1$ and $D_2$ receptors in the present study, one may propose that activation of the dopamine receptors by HA causes memory deficit. Furthermore, due to the major effects of HA on inhibition of $MAO_A$ and $_B$ (Glennon et al., 2000), and the elevated level of dopamine in the synaptic clefs, learning and memory may be impaired. In agreement with our results it has been shown that the $D_1$ receptor antagonist, SCH23390 (Hyttel, 1984) and a high doses of $D_2$ receptor antagonist, sulpiride (Stoof and Kebabian, 1984) reversed the amnesia induced by dopamine receptor agonist, apomorphine, suggesting that both dopamine $D_1$ and $D_2$ receptors antagonists are involved in the retrieval deficits. Moreover, the study revealed that pre-synaptic dopamine receptor activation is able to improve memory retrieval. In contrast, post synaptic dopamine receptor stimulation impairs memory retrieval (Ichihara et al., 1988). On the other hand, our data showed that the higher dose of the antagonists in the presence of HA affect exploratory behaviors, showing anxiogenic-like effect, which may be due to dopamine receptor antagonists by themselves.

Our data also indicated that pre-test single administration of different doses of SCH23390 or sulpiride in doses used, caused no significant change in the step-down latency. The results are in agreement with our previous study that peripheral injection of the $D_1$ and $D_2$ receptor antagonist induced no effect in step-down test in mice (Rezayof et al., 2006). However, other investigations indicated that intra-dorsal hippocampus (Rezayof et al., 2007) and peripheral (Adriani et al., 2000; Coccurello et al., 2000) administration of the antagonists impaired the one-trial passive avoidance and spatial and non-spatial memories in mice, respectively. The controversial results may be due to methods, route of administration and/or the doses of drugs used.

In the present study, the higher doses of the antagonists decreased head-dip, suggesting anxiogenic-like behaviors. In agreement with our data, some studies have indicated that administration of antagonists induce anxiogenic-like behavior in animals (Russell et al., 1987; Sanberg, 1989). There are also data indicating that stress activates the mesolimbic dopamine system (Bonnet and Costentin, 1986; Kalivas and Abhold, 1987), and an increase in the dopamine in the synaptic cleft, e.g. by inhibition of dopamine reuptake which may induce anxiety-like behavioural effects (Duterte-Boucher et al., 1990; Simon et al., 1993). In addition, other evidence suggested that dopamine $D_1$ receptors agonist, SKF38393 and the antagonist SCH23390 did not show anxiolytic-like or even anxiogenic effect in other animal models (Johnston and File, 1989; Rodgers et al., 1994; Simon et al., 1993). In some animal models of anxiety, $D_2$ dopamine receptor antagonist, haloperidol has been demonstrated to induce anxiolytic-like activity (Pich and Samanin, 1986), however, these results have not been confirmed by others (Barrett et al., 1991; Talalaenko et al., 1994; Witkin and Perez, 1989).

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