Global Veterinaria 15 (6): 605-612, 2015
ISSN 1992-6197

DOI: 10.5829/idosi.gv.2015.15.06.101156

Anxiolytic Effects of Harmine Injection on Elevated Plus-Maze Behavior in Male Wistar Rats

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Abstract: The aim of this study is to determine the effect of acute administration of β carboline harmine on the behavioral of rats exposed to chronic mild stress (CMS) procedure. To develop this study we used 60 animals divided into six groups as follows: (G1) non- stressed- Saline. (G2) non-stressed-Amitriptyline; (G3) non- stressed - Harmine; (G4) stressed- Saline; (G5) stressed-Amitriptyline; (G6) stressed- Harmine. After 30 days of exposure to CMS, rats were treated with harmine (15 mg/kg/day) and amitriptyline (20 mg/kg) for 7 days. After treatment period, the rats were subjected to the elevated plus- maze test and sucrose preference test (SPT). Our results demonstrated that CMS procedures induced anhedonia, a decrease in the number of entries and time spent in the open arms without affecting the number of entries either the time spent in closed-arms on EPM apparatus. Harmine and Amitriptyline treatment reversed anhedonia, increased the number of entries and the time spent on open arms. Finally, we concluded that harmine could be used to improve depressive disorders.

Key words: Harmine · Cms · Anhedonia · Epm

INTRODUCTION

Anxiety is a frequent consequence of chronic stress. In humans, stressful life events may lead to anxiety even in the absence of a chronic physiological stress response [1]. Many studies have been conducted to identify the role of different factors that contribute to the development of depression and anxiety [2, 3].

It has been reported that anxiety related behavioral alterations which induced in humans and animals, so it could be explained by change in the neuroendocrine mechanisms [4]. Exposure to stress is a main environmental risk factor associated with the occurrence of depression [5-7]. It's may be the most important environmental factor affecting feeding behavior, metabolism and neuroendocrine functions [8, 9]. Among trusty models of depression, chronic mild stress (CMS) model of depression in rodents has been proposed to model some of the environmental factors that contribute to the introduction of depressive disorders in humans [10]. In the present protocol, CMS sequential exposure of rats to a variety of mild stressors causes behavioral changes which can be related with a modifications of the HPA axis [11-14]. The sucrose-intake deficits is a condition which could be reversed by the chronic administration of classical antidepressant drugs at the same time as dopaminergic agonists the chronic administration of classical antidepressant [15-18]. These changes develop gradually over time with combination of mild, unpredictable stressors and suggest improved face validity of this compared with the more acute stress models. Construct validity for CMS is largely based on the development of reduced sucrose preference, which is interpreted to reflect anhedonia, a core symptom of

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depression [19]. Therefore a many studies concerning to identify a new substance that can potentially treat anxiety disorders and depression [20, 21]. Studies have proved that β-carboline alkaloids, like harmane, norharmane, harmine and others, display antidepressant actions in mouse subjected to forced Swimming test as an animal model of depression [22]. The B carboline harmine was first isolated in 1847 from seeds of *Peganum harmala* and *Banisteriopsis caapi*, both of which have traditionally been used for ritual and medicinal preparations in the Middle East, Central Asia and South America [23]. There are many reports showing the antioxidative action [24, 25] and the inhibition of monoamine oxidase [24].The results of above studies suggest a possible importance of β-carbolines in control of depressive states. Considering this background, the current study was carried out to investigate the antidepressant effects of β-carbolines harmine in rats exposed to chronic mild stress (CMS), generally used behavioral model to induce depressive like state [26, 27] also to investigate the impact of this dose on rats behavior.

MATERIAL AND METHODS

Animals: Male Wistar rats were obtained from the Pasteur institute of Algiers, that weighed 200-340 g they were housed ten per cage with food and water available *ad libitum* and they were maintained at natural conditions (Temperature and a relative humidity). Before the initiation of the experiment. Animals were weighted and separated into six groups, as follows: (1) control-saline (1ml/kg), (2) control-amitriptyline (20mg/kg); (3) control- harmine (15mg/kg); (4) stressed - saline (1ml/kg); (5) stressed-amitriptyline (20mg/kg); (6) stressed- harmine (15mg/kg). Animals in the control group were reared in single cages without any environmental stresses unlike animals in CMS were entered into the CMS procedure.

Drugs: Harmine was obtained from Cayman Chemical (USA) in dose of 15 mg / kg and amitriptyline, the standard antidepressant, from Gencopharm (ZI Rouiba, Route C BP 73, Algeria).was injected intraperitoneally once per day during 7 days. After CMS procedure, different groups of rats (n=10 each) were administered intraperitoneally (i.p.) with saline, harmine (15 mg/kg) or amitriptyline (20 mg/kg) before 30 min of the test session elevated plus maze to assess the behavior of rats and the possible effects of treatment. All treatments were administered in a volume of 1mL/kg.

Chronic Mild Stress Procedure: The chronic mild stress protocol was adapted from a several studies [26] with some modification. This model used to achieve depressive-like symptoms in Wistar rats [28, 29]. Also it is used for screening novel antidepressant treatments and investigating the neurobiology of depression and its relation to other diseases [29, 30]. During this experiment, the rats in the control group were kept unperturbed, in their home cages without any stress, receiving only ordinary daily care with daily supports of food and water, whereas the CMS groups were subjected to different mild stressors, applied randomly for 30 days. Briefly, The following stressors were used: (i) forced swimming for a duration of 10 or 15 min on days 1, 15, 21, 25 ;(ii) 24 h water deprivation on days 5, 10, 14,19,30 ; (iii) 24 h food deprivation was applied on days 6, 13, 20,26; (iv) 1–1,5 h restraint on days 2,3,4,7,8,9 and 2-3-4 h restraint on days 16-29,(v) and no-stress on days 11-12-27. Restraint stress is based on that of Bardin *et al*. [31] FST is formed on that of Porsolt *et al*. [32].

Elevated plus Maze (EPM): The elevated plus maze has strong claims to validity as an animal model of anxiety, The apparatus and the testing procedure were carried out as originally described by Pellow and associates [33]. The EPM apparatus was made of wood and consisted of Two opposite open arms (50×10 cm) had no walls and the other two closed arms (50×10 cm) had 50 cm high walls made of clear Plexiglas. The model is based on rodents' aversion of open spaces. The open and closed arms were connected by a central square (10×10 cm) and were elevated 50 cm above the floor. Rats from each group were placed in the central square of the Plus-Maze facing an open arm and were then allowed to explore the apparatus. And their activity was videotaped for 5 min. The following behaviors were scored during the test: the number of entry in each arm, Time spent in the open and closed arms, while the numbers of entries into the open and closed arms were mostly used as measures of general activity [34, 35]. An individual entry was recorded when the animal entered the arm with at least two front paws and half of its body. The shorter is the times spent in open arms, the higher is anxiety and vice versa [36, 37]. After 5 minutes, rat were removed from the maze by the base of their tails and returned to their home cage. The maze was than cleaned with a solution of 30% ethanol and soft paper permitted to dry between tests.

Sucrose Preference Test (Anhedonia Test): Sucrose preference (SP) test is a measure to evaluate anhedonic effect of CMS [29, 38]. In this test, rats were trained access to two bottles (Water and 1% sucrose solution) freely for 7 days. The position of the 250-mL bottles containing sucrose solution or tap water was changed every day. Sucrose preference was expressed as percent of the volume of sucrose solution of a total volume of fluid (Sucrose plus regular water).

Data Analysis: The Statistical Minitab 16.0 was used for statistical analyses. All data are presented as mean±S.E.M. Differences among experimental groups were determined by one-way ANOVA followed by Tukey's post hoc test. *p* Values less than (0.05) were considered statistically significant.

RESULTS

The Results of Various Tests Are Discussed Below: Data regarding to the effect of acute administration of harmine on the behavioral changes during the elevated plus- maze were outlined in Figure (1.A, B). The number of entries and time spent in open arms were significantly affected by amitriptyline and harmine treatment (P<0.05, P <0.01). Which CMS rats displayed decrease in the number of entries and in the time spent in the open arms compared to non-stressed rats Figure 1A,B [F(2,70-4,14), P =(0.030-0.003)]; Moreover, No significant differences were detected for rats treated with amitriptyline or harmine compared with control rats on the number of entries and the time spent in closed arms ([F(2,15-1,36), (P=0.074-0,252]) Figure (1C ;D) (P >0.05).

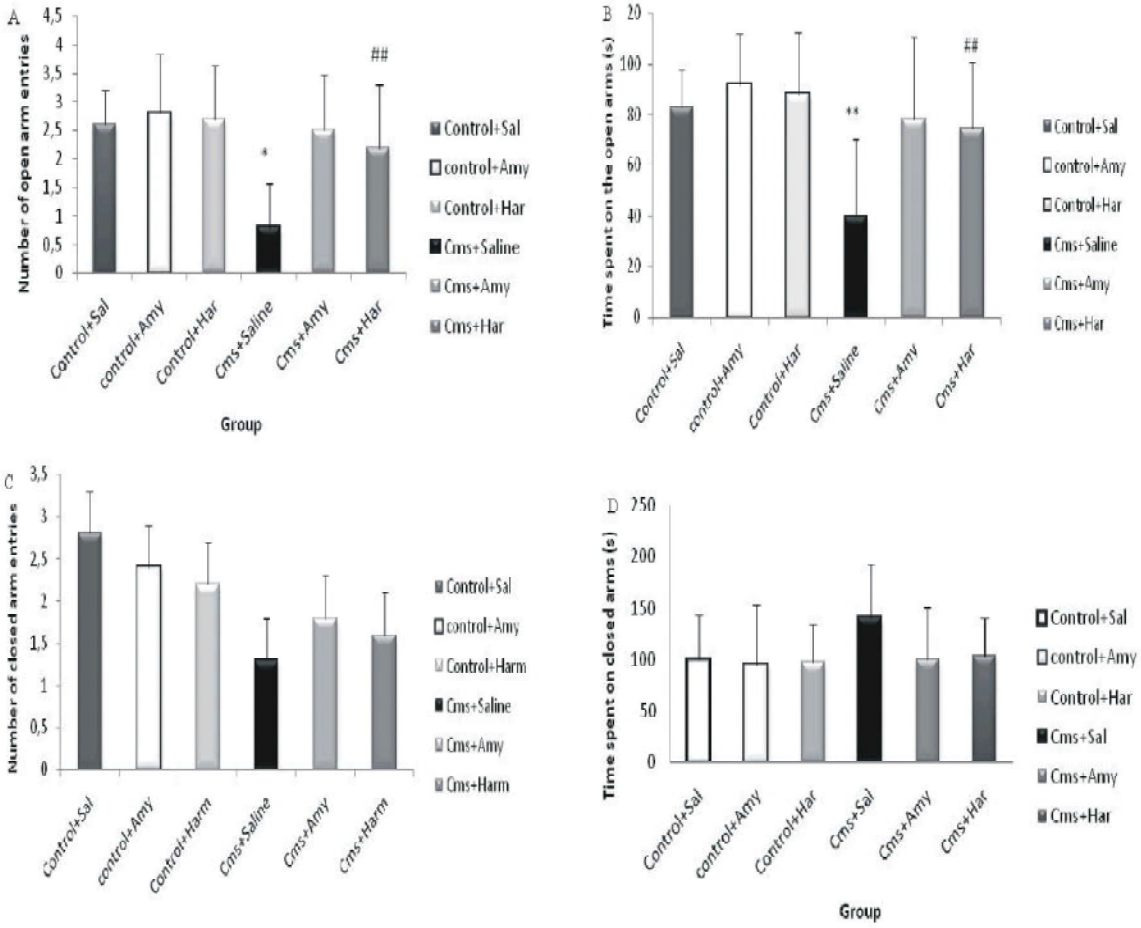

Fig. 1: Effects of CMS procedure on the number of entries in open arm (A) On the Time spent in open arms (B) on the number of entries in closed arms (C) and on the time spent in closed arms (D) in the Elevated plus maze test in rats repeatedly treated with amitriptyline or harmine. Bars represent means±S.E.M. * p<0, 05 vs. control saline; # p<0.05 vs.CMS saline, according to ANOVA post-hoc Tukey test.

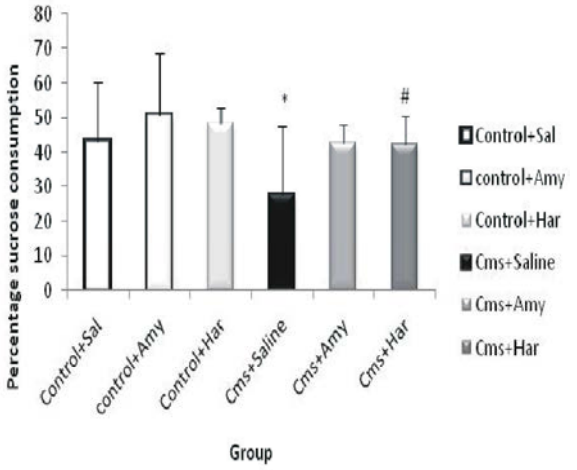

Fig. 2: Effects of CMS procedure on sweet food consumption in rats treated with amitriptyline or harmine. Bars represent means±S.E.M. * p<0, 05 vs. control saline; # p<0.05 vs.CMS saline, according to ANOVA post-hoc Tukey test.

As shown in Fig. 2, CMS rats treated with saline reduced sucrose solution consumption compared with non-stressed rats treated with saline (P <0.05). Statistical analysis revealed that CMS rats treated with harmine reverted the reduction of sucrose solution consumption induced by chronic mild stress ([F=3, 27), P =0.012]).

DISCUSSION

The present data clearly suggest that intraperitoneally injection of harmine decreased the level of anxiety that appeared in the behavior change induced by chronic stressful stimuli.

When behaviors were assessed, we found that the number of entries and the time spent on the open arms were significantly changed by stress, so administration of harmine reversed the behavior induced by chronic stressful stimuli that induced an increase of the number of entries and the time spent in the open arms apparatus. According to these results, in rats application of chronic mild stress (CMS) procedures resulted in a variety of behavioral, neurochemical, neuroendocrine and neuroimmune alterations resembling some of the dysfunctions observed in human depression [39-42].

The elevated plus-maze test is based on the spontaneous exploratory behavior of rodents and their natural aversion to the open arms caused by fear and anxiety [33, 43]. Which, an increase in the number of entries added to the lengthy time spent in the open arms apparatus demonstrate a lower level of anxiety [43, 44].

This finding suggests that seven days of treatment with harmine and amitriptyline (15-20 mg/kg) are significantly caused anti-anxiety-like effect, which is consistent with a previous study [45-49] on the other hand both of harmine and amitriptyline did not enhance the change in locomotor activity in the closed arms. Whereas other antidepressant such us venlafaxine treatment significantly caused anti-anxiety-like effect and also improved locomotor activity [50].

The difference from previous studies may result from possibly milder stress applied in our CMS protocol, experimental procedures (Day-night phase of the application of stress and age of the animal) may affect the behavior of the animal.

The CMS paradigm is a model of depression which induces by chronic mild and unpredictable stressors [33]. In the CMS model, both of sweet food consumption and preference sucrose intake, as well as decreased intracranial self stimulation behavior, serves as markers of generalized decrease in sensitivity to reward and they are quite related to anhedonia [27, 51, 52]. In accordance with the literature, present data confirm that rats subjected to CMS procedure consume less sweet food compared to non-stressed rats treated with saline [53-57]. These findings suggest that, under our experimental conditions, the CMS procedure induced anhedonic-like behavior in our rats.

The present findings demonstrate that repeated administration of harmine reversed the anhedonic-like behavior in CMS rats and increased sweet food consumption in non-stressed rats. In this study, The behavioral effects induced by harmine in rats are in coincidence with the literature data, which support an antidepressant action for harmine in basic studies that could be due to interactions of harmine and related alkaloids with several receptor systems act as agonists at serotonin receptors [58-60] involved in the modulation of behavioral and molecular actions of antidepressants [25, 59, 61, 62]. ß carbolines, mainly harmine and harmaline, inhibit MAO activity [63] Furthermore, as MAO inhibitors, ß-carbolines can increase the level of serotonin in the brain [64] and are capable of inducing direct psychoactive effects [65,66]. Brierley *et al*. [67] also suggested that harmine increase dopamine efflux via a novel shell-specific, presynaptic 5-HT2A receptor dependent mechanism, independent of MAO inhibitory activity.

Consistent with previous studies in which 40 day of CMS and in the forced swimming test significantly induced depressive-like behavior in rats [22, 68] the results of our study also showed that chronic mild stress induced significant depressive-like behavior, including decreased sucrose solution intake.

CONCLUSION

From the above observations we can conclude that acute administration of harmine develops anxiolytic activity & Anti depressant at both the dose level which is comparable with the standards. Which prevents the development of anxiety/depressive-like behavior in CMS rats. However further studies are required to know the exact mechanism action of harmine as anxiolytic.

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