



AGMATINE AMELIORATES SOCIAL ISOLATION INDUCED OBSESSIVE-COMPULSIVE BEHAVIOR IN MICE

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ABSTRACT

Obsessive-compulsive disorder (OCD) is a neuropsychiatric condition characterized by persistent intrusive thoughts (obsessions), repetitive ritualistic behaviors (compulsions) and excessive anxiety. Obsessive-compulsive disorder is classified as an anxiety disorder under DSM-IV-TR guidelines. In OCD, the levels of serotonin and nitric oxide decreased; whereas levels of dopamine and glutamate increased in brain. Environmental conditions such as isolation from social surroundings lead to anxiety and increased level of aggression. The present study was designed to examine the effect of agmatine in social isolation induced obsessive-compulsive behavior on marble burying behavior and locomotor activity. Agmatine (20, 40 and 80 mg/kg, i.p.) was administered in different groups of mice; activity was observed 30 min after dosing. Acute treatment of agmatine (40 and 80 mg/kg, i.p.) significantly reduced marble burying behavior. Moreover, hyperlocomotion was observed in socially isolated animals and agmatine was found to attenuate the same without affecting basal locomotions. In conclusion, agmatine effectively decreases social isolation induced obsessive-compulsive behavior in mice.

Keywords: Agmatine, social isolation, marble-burying behavior, locomotor activity, Obsessive-compulsive behavior

INTRODUCTION

Obsessive-compulsive disorder (OCD) is defined as recurrent and persistent thoughts, impulses (obsession) and/or repetitive purposeful behaviors (compulsions)^[1]. 1- 3% of children and adults are suffering from this condition^[2]. There are evidences that increased OCD symptom severity has been linked with diminished quality of life^[3] and also increased functional impairment.

Social isolation is defined as a state in which the individual lacks a sense of belonging socially, lacks engagement with others, has a minimal number of social contacts and they are deficient in fulfilling and quality relationships^[4]. Social isolation (SI) causes a variety of behavioral changes like hyper-locomotion, anxiety, impulsivity, aggression. These behavioral abnormalities in rodents may be related to the symptoms in patients with neuropsychiatric disorders such as attention-deficit hyperactivity disorder, obsessive-compulsive disorder, autism, schizophrenia, depression. In addition, Social isolation and OCD are associated with similar neurochemical changes like hypofunction of serotonin, dopamine and glutamate hyperfunction^[5]. These changes might be one of the causes for exacerbation of OCD in

social isolation. Agmatine [4- (amino butyl) guanidine] is an endogenous amine, widely present in mammalian brain and proposed as a novel neurotransmitter in the central nervous system^[6]. It is a metabolite of L-arginine via arginine decarboxylase and hydrolyzed to putrescine and urea by agmatinase. Recently, Agmatine is evidenced for anti-compulsive like effect^[7]. It has also been reported for its effectiveness in schizophrenia^[8], addictive behavior^[9], stress^[10], anxiety^[11] and depression^[12]. Besides this, Agmatine is evidenced for modulating levels of serotonin^[13] as well as dopamine and glutamate levels^[14]. Incidentally, these neurotransmitters levels are altered in social isolation and OCD.^[14] Hence, in the present study, the effect of agmatine was investigated in social isolation induced OCD in mice.

MATERIALS AND METHODS

Experimental Animals

Adult male albino Swiss mice (22–25 g) were group housed (n=6) under a standard 12 h light/dark cycle and controlled conditions of temperature (23 ± 2°C) and humidity (55 ± 10%). Mice were acclimatized to laboratory conditions for 7 days before carrying out the experiments. The animal studies were approved by the Institutional Animal Ethics Committee (IAEC) (SCOP/IAEC/2013/14/151).

Drugs

Agmatine sulfate was purchased from Sigma-Aldrich Ltd., USA. Drug solutions were prepared fresh and doses are expressed in terms of their free bases.

Isolation condition

Mice were housed singly in cages (21 x 38 x 14 cm) under a controlled 12-hour/12-hour light-dark cycle,

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with a room temperature of $23\pm 2^{\circ}\text{C}$ and humidity of $55\pm 10\%$. All efforts were made to minimize suffering^[15].

Assessment of marble-burying behavior

Marble-burying behavior (MBB) is considered to be a potential model of OCD based on behavioral similarities^[16]. Briefly, after 3 weeks of isolation mice were placed individually in plastic cage ($21\times 38\times 14$ cm), containing 5 cm thick sawdust bedding. Twenty small glass marbles (diameter 10–12 mm) were arranged on the bedding evenly spaced in four rows. Mice were exposed to marbles for 30 min without food and water; thereafter, the unburied marbles were counted. A marble was considered “buried” if two-third of its size was covered with saw dust. The number of marbles buried was considered as an index of compulsive behavior. The number of marbles buried during 30 min was analyzed by observer who was blind to treatment groups.

Assessment of locomotor activity

Locomotor activity was carried out after 3 weeks of isolation to evaluate whether effect of drug on MBB was not associated with changes in motor activity. Locomotor activity was measured using open field test apparatus^[17]. Each mouse was treated with drug and after 30 min it was placed at the center of the open field test apparatus, the floor divided into 25 squares, and monitored for 8 min. The number of crossings was scored to evaluate the locomotor activity.

Statistical analysis

The Data presented here was analyzed by one way analysis of variance (ANOVA) followed by Tukey’s test for multiple comparisons. Data was expressed as a mean \pm S.E.M and value of $P < 0.05$ was considered to be statistically significant in all the cases.

RESULTS

Dose dependent study of acute agmatine on marble burying behavior and locomotor activity

Acute treatment of agmatine (20, 40 and 80 mg/kg, i.p.) in mice dose dependently decreased the marble-burying behavior [$F(3, 20) = 135.2, P < 0.0001$]. Tukey’s test indicated that agmatine (20, 40 and 80 mg/kg, i.p.) significantly decreased burying behavior when compared to the saline treated group (Fig 1). Moreover, there is no significant difference between doses of 40 mg and 80 mg. However, locomotor activity at all these doses was remained unaffected [$F(3, 20) = 0.7478, P = 0.5363, P > 0.05$], when compared to the saline treated group (Fig 2).

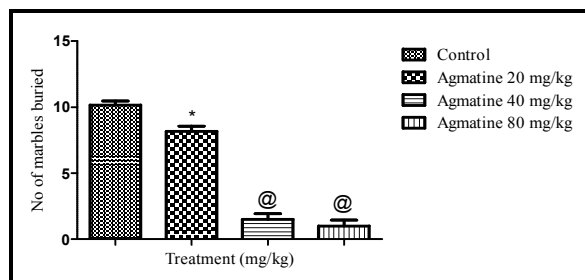


Figure 1: Dose dependent study of acute agmatine on marble burying behavior

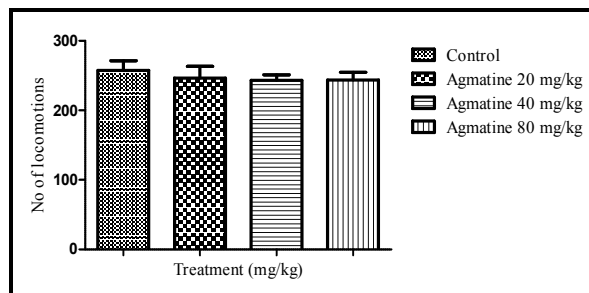


Figure 2: Dose dependent study of acute agmatine on locomotor activity

Effect of acute treatment of agmatine on marble burying behavior and locomotor activity in socially isolated mice

Acute treatment with agmatine (40 and 80 mg/kg, i.p.), dose dependently inhibited the increased marble burying behavior in social isolation state [$F(4, 25) = 254.0, P < 0.0001$] (Fig 3). In addition, agmatine (40 and 80 mg/kg, i.p.) attenuated hyperlocomotion in social isolation state without affecting basal locomotions in mice [$F(4, 25) = 8.891, P < 0.0001$] (Fig 4) when compared to social isolation group. However, lower dose of agmatine (20 mg/kg, i.p.) was found to have no significant effect on social isolation induced marble burying behavior and hyperlocomotions ($P = 0.9606$) (Fig. 4).

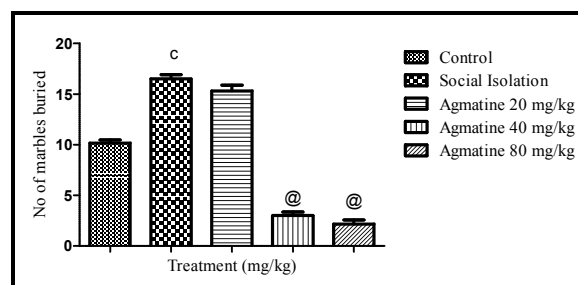


Figure 3: Effect of acute treatment of agmatine on marble burying behavior in socially isolated mice

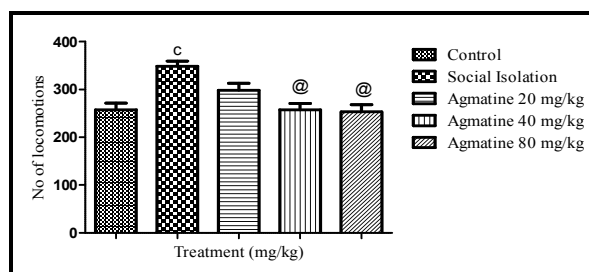


Figure 4: Effect of acute treatment of agmatine on locomotor activity in socially isolated mice

Effect of chronic treatment of agmatine on marble burying behavior and locomotor activity in socially isolated mice

Chronic treatment with agmatine (40 and 80mg/kg, i.p.) to experimental (social isolated) group, significantly ($P < 0.001$) prevented the increased marble-burying behavior [$F(3, 20) = 51.10, P < 0.0001$] when compared to social isolation group without treatment. However, chronic treatment of higher dose (80mg/kg, i.p.) was found more effective (Fig 5) when compared to chronic agmatine (40 mg/kg, i.p) treated group. One-way ANOVA revealed that chronic treatment of agmatine (40 and 80 mg/kg, i.p) significantly prevented increase in locomotor activity (without affecting basal locomotions) in socially isolated mice, [$F(3, 20) = 13.99, P < 0.0001$] (Fig 6).

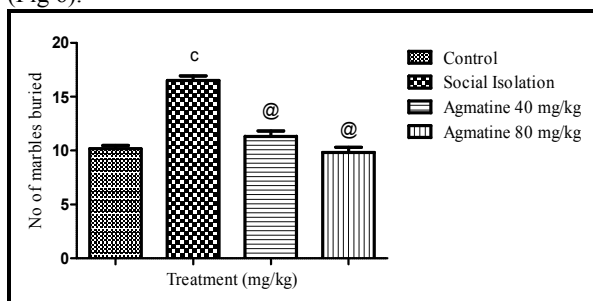


Figure 5: Effect of chronic treatment of agmatine on marble burying behavior in socially isolated mice

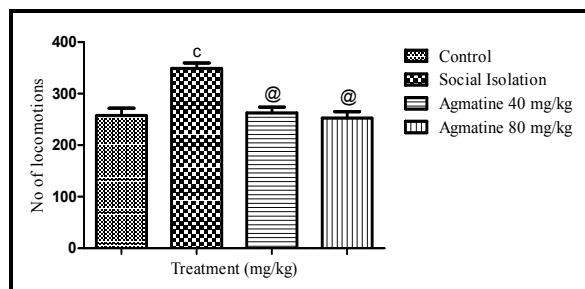


Figure 6: Effect of chronic treatment of agmatine on locomotor activity in socially isolated mice

DISCUSSION AND CONCLUSION

The current study revealed that agmatine ameliorates social isolation induced obsessive-compulsive behavior in mice. Acute treatment of agmatine dose dependently decreased increased marble burying behavior as well as chronic treatment prevented increase in marble-burying behavior evident in social isolation state. This is the first study to report the effect of agmatine in social isolation state.

The present study reported that three weeks (21 days) of isolation exacerbates marble burying behavior when compared to normal control mice. Social isolation has been reported for serotonin dysfunction^[18] and also for hyperactivity of dopamine and glutamate^[19]. Moreover, similar neurotransmitters changes are also reported in OCD.

Marble burying behavior is most representative animal model of OCD. In present investigation, agmatine significantly decreased MBB in mice without altering basal locomotions. Further, effect of acute and chronic treatment of agmatine was studied in social isolation induced obsessive-compulsive behavior. Acute treatment with agmatine (40 and 80 mg/kg, i.p.) on day 22 at 9.00 h, in socially isolated animals significantly decreased increased marble burying behavior when compared to socially isolated group. Acute agmatine 20 mg/kg, i.p. was found ineffective in reducing social isolation induced obsessive-compulsive behavior when compared to socially isolated animals. Social isolation (3 weeks) is already reported for producing hyperlocomotions in mice^[15]. The same effect was observed in present study. Furthermore, it was also observed that acute agmatine significantly reduced hyperlocomotions in social isolated animals.

Moreover, chronic treatment of agmatine (40 and 80 mg/kg, i.p.) in social isolation state, significantly prevented an increase in marble-burying behavior after 3 weeks of isolation in animals. In addition, chronic treatment of agmatine also prevented an increase in locomotor activity due to social isolation without affecting basal locomotions when compared to socially isolated animals. However, present study revealed that the influence of agmatine on marble-burying behavior was same after acute as well as chronic treatment.

It has been evidenced that decreased social behavior in rats is associated with high level of dopamine levels^[20]. On the other hand, low level of serotonin has been reported in the social isolation state^[18]. Interestingly, agmatine is reported to have role on serotonin, dopamine and glutamate neurotransmitters. To support, large numbers of experimental and clinical studies indicated that the serotonin system is strongly implicated in the neural regulation of mood and several evidences shows abnormalities of serotonin neurotransmission in the pathophysiology of depression and agmatine reported to increase serotonin levels in anti-depressant like activity in mice^[13]. Recently, agmatine reported to mediate anti-compulsive like effect through imidazoline binding sites and suggested involvement of these binding sites in OCD^[7].

In conclusion, present study demonstrated anti-compulsive effect of agmatine in social isolated mice. This state aggravates marble-burying behavior in mice and acute as well as chronic treatment of agmatine attenuates the same. These effects of agmatine might be due to modulation of serotonergic; dopaminergic and glutamatergic systems as well as through binding sites which are reported for their involvement in OCD. Future studies are aimed to understand possible mechanism of actions of agmatine for its anti-compulsive like effect in OCD as well as social isolation induced OCD.

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