

Study of Agomelatine for the Reduction of Marble Burying Behavior in Brain Disorder

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ABSTRACT

Obsessive-Compulsive Disorder (OCD) is a debilitating disease which is characterized by persistent thoughts (obsessions), which are associated with seemingly purposeful ritualistic behavior (compulsions). The effect of acute and chronic administration of agomelatine on the marble-burying behavior (MBB) of mice, which is reported to be an index of anticompulsive behavior, was performed. Results indicated a potent and dose dependent influence of agomelatine on MBB of mice, which was maintained after its chronic administration. However, the higher doses (40 and 50 mg/kg) were found to be locomotor depressant. Treatment with PCPA was not able to inhibit the effect of agomelatine on marble-burying behavior. In conclusion, agomelatine administration reduces the MBB in mice, which should be explored for its potential use in the treatment of OCD.

Keywords: Obsessive Compulsive Disorder (OCD), Agomelatine, Marble Burying Behavior (MBB), Locomotor Count (LC).

INTRODUCTION

Obsessive compulsive disorder (OCD) involves severe alterations in thought processes and behavior. Its core features are intrusive and persistent thoughts that cause distress (obsessions), and compulsions, which are performed in order to alleviate this distress. Obsessions and compulsions are typically egodystonic, that is, the person is consciously aware that they are abnormal, yet cannot control them. Many people experience obsessive-like thoughts and/or compulsive-like behavior, but what distinguishes obsessions and compulsions of OCD is their frequency and intensity.

OCD is characterized by high rates of partial and/or absent response to standard, recommended treatments, often prompting pharmacological and non-pharmacological augmentation or switching of strategies. Functional neuroimaging of subjects with OCD has revealed abnormalities in corticostriatal-thalamo-cortical circuits, involving the orbitofrontal cortex (OFC), anterior cingulate gyrus, insula,

striatum and thalamus. These studies are consistent with the existence of distinct OCD symptom dimensions, as contamination/washing, checking and hoarding subgroups show different patterns of brain activity^{2,3}.

One of the recent drugs used for the treatment of depression is agomelatine which happen to be a nonselective melatonin agonist. It has high-affinity for MT1/MT2 melatonin receptors and is also a 5-HT_{2C} serotonin receptor antagonist. Agomelatine does not directly affect the uptake of serotonin, norepinephrine or dopamine. By inhibiting 5HT-2C receptors, however, it secondarily increases norepinephrine and dopamine in the frontal cortex of the brain. This effect might contribute to its antidepressant activity. In view of these evidences, it appears that compulsive behavior might be modulated by OCD melatonergic system and hence this study aims to investigate the role of melatonergic system on the modulation of compulsive behavior in rodents.^{4,5}

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MATERIAL AND METHODS^{6,7}

Adult male albino Swiss mice (22-25 g), were used for the present study. The animals were group housed [mice (n=6)] under a standard 12h light/dark cycle and controlled conditions of temperature and

humidity ($25\pm 2^{\circ}\text{C}$, 55-65%). All animals were acclimatized to laboratory conditions for at least seven days before carrying out the experiments, which were carried at 08.00 to 15.00 h daily. Separate group of mice ($n=6/12$) was used for each set of experiments. Agomelatine and DL-4-chlorophenylalanine (PCPA, a selective serotonin depletor) were purchased from Sigma-Aldrich. Agomelatine was dissolved in 1% hydroxyl ethyl cellulose while fluoxetine was dissolved in 0.9% saline solution and pcpa was dissolved in propylene glycol.

Volume of drug administration

The volume of administration of drug vehicle was calculated based upon the body weight of mice i.e 10 ml/kg body weight of mice.

Apparatus: Marble-burying behaviour test apparatus

It consisted of plastic cages ($40 \times 28 \times 14$ cm) containing 5 cm thick wood dust bedding. Twenty small glass marbles (~10 mm), were arranged on the bedding evenly spaced in four rows of five each. The cage was covered by transparent plastic lead with line markings (2×2) and the apparatus is placed 1.5-2.0 m below a video camera in the experiment room with bright light (100 lux).



Figure 1: Marble burying behaviour of mice

Experimental methods

Assessment of marble-burying behavior and motor activity in mice

The marble-burying behavior and locomotor of mice was recorded as reported by Umathe et al., earlier with slight modifications. In brief, mice were individually placed in marble-burying behavior apparatus with 20 glass marbles for 30 min. The

behavior of the mice during the test session was recorded by a video camera. At the end mice were removed, and unburied marbles were counted. A marble was considered 'buried' if its two-third size was covered with saw dust. The total number of marbles buried was considered as an index of obsessive-compulsive behavior. The video recording was analyzed to determine the number of line crossings made by the animal during a test session. Total number of line crossings measured during 30 min was considered as locomotor counts for the animals.

Effect of agomelatine (10mg/kg, i.p.) on marble burying behavior

The effect of agomelatine at the dose of 10 mg/kg on marble burying behavior was evaluated. The weight of mice varies between 21.13 g to 23.92 g and the dose of agomelatine was calculated on the basis of their body weight of each mouse. Total six cages were taken in the study and in each cage one mouse was taken. The time spent by each mouse in each cage was 30 minutes.

The number of marble buried in each cage was evaluated in all the six cages and for each animal. In the case of first cage the total no. of marble buried was found to be 11, in second one it was 09 and in the case of third, fourth, fifth and sixth, cage it was found to be 07, 04, 13 and 11 respectively. The results indicate that the highest number of marble buried was found to be in the cage number fifth.

Table 1: Effect of agomelatine (10 mg/kg, i.p.) on marble burying behavior

S. No.	Cage No.	Wt. of mice (g)	No. of male mice	Time spend in cage (min.)	No. of marble buried
1	I	21.86	01	30	11
2	II	22.64	01	30	09
3	III	21.22	01	30	07
4	IV	23.92	01	30	04
5	V	22.22	01	30	13
6	VI	21.13	01	30	11

Effect of agomelatine (20mg/kg, i.p.) on marble burying behavior

The effect of agomelatine at the dose of 20 mg/kg on marble burying behavior was evaluated. The weight of mices varies between 20.23 g to 24.82 g and the dose of agomelatine was calculated on the basis of their body weight of each mouse. Total twelve cages were taken in the study and in each cage one mouse was taken. The time spent by each mouse in each cage was 30 minutes. The number of marble buried in each cage was evaluated in all the twelve cages and for each animal.

In the case of first cage the total no. of marble buried was found to be 9, in second one it was 07 and in the case of third, fourth, fifth, sixth, seven, eight, nine, ten, eleven and twelve cage it was found to be 06, 11, 08, 07, 06, 05, 06, 09, 11 and 07 respectively. The results indicate that the highest number of marble buried was found to be in the cage number fourth and sixth.

Table 2: Effect of agomelatine (20 mg/kg, i.p.) on marble burying behavior

S. No.	Cage No.	Wt. of mice (g)	No. of male mice	Time spend in cage (min.)	No. of marble buried
1	I	21.22	01	30	09
2	II	21.86	01	30	07
3	III	22.92	01	30	06
4	IV	23.92	01	30	11
5	V	20.78	01	30	08
6	VI	22.19	01	30	07
7	VII	23.92	01	30	06
8	VIII	22.64	01	30	05
9	IX	24.82	01	30	06
10	X	22.75	01	30	09
11	XI	20.23	01	30	11
12	XII	20.78	01	30	07

Effect of agomelatine (30 mg/kg, i.p.) on marble burying behavior

The effect of agomelatine at the dose of 30 mg/kg on marble burying behavior was evaluated. The weight of mices varies between 20.63 g to 23.73 g and the dose of agomelatine was calculated on the basis of their body weight of each mouse. Total twelve cages were taken in the study and in each cage one mouse was taken. The time spent by each mouse in each cage

was 30 minutes. The number of marble buried in each cage was evaluated in all the twelve cages and for each animal.

In the case of first cage the total no. of marble buried was found to be 11, in second one it was 09 and in the case of third, fourth, fifth, sixth, seven, eight, nine, ten, eleven and twelve cage it was found to be 08, 07, 03, 11, 07, 05, 07, 02, 06 and 03 respectively. The results indicate that the highest number of marble buried was found to be in the cage number fourth and sixth.

Table 3: Effect of agomelatine (30 mg/kg, i.p.) on marble burying behavior

S. No.	Cage No.	Wt. of mice (g)	No. of male mice	Time spend in cage (min.)	No. of marble buried
1	I	21.22	01	30	11
2	II	21.86	01	30	09
3	III	22.92	01	30	08
4	IV	23.73	01	30	07
5	V	20.78	01	30	03
6	VI	22.19	01	30	11
7	VII	20.78	01	30	07
8	VIII	20.63	01	30	05
9	IX	21.27	01	30	07
10	X	22.34	01	30	02
11	XI	20.78	01	30	06
12	XII	21.92	01	30	03

Effect of agomelatine (40 mg/kg, i.p.) on marble burying behavior

The effect of agomelatine at the dose of 40 mg/kg on marble burying behavior was evaluated. The weight of mices varies between 20.78 g to 23.92 g and the dose of agomelatine was calculated on the basis of their body weight of each mouse. Total six cages were taken in the study and in each cage one mouse was taken. The time spent by each mouse in each cage was 30 minutes. The number of marble buried in each cage was evaluated in all the six cages and for each animal. In the case of first cage the total no. of marble buried was found to be 08, in second one it was 13 and in the case of third, fourth, fifth and sixth, cage it was found to be 07, 06, 07 and 09 respectively. The results

indicate that the highest number of marble buried was found to be in the cage number second.

Table 4: Effect of agomelatine (40 mg/kg, i.p.) on marble burying

S. No.	Cage No.	Wt. of mice (g)	No. of male mice	Time spend in cage (min.)	No. of marble buried
1	I	22.64	01	30	08
2	II	20.78	01	30	13
3	III	21.22	01	30	07
4	IV	23.92	01	30	06
5	V	22.34	01	30	07
6	VI	21.46	01	30	09

Effect of agomelatine (50 mg/kg, i.p.) on marble burying behavior

The effect of agomelatine at the dose of 50 mg/kg on marble burying behavior was evaluated. The weight of mices varies between 20.63 g to 23.92 g and the dose of agomelatine was calculated on the basis of their body weight of each mouse. Total twelve cages were taken in the study and in each cage one mouse was taken. The time spent by each mouse in each cage was 30 minutes. The number of marble buried in each cage was evaluated in all the twelve cages and for each animal.

In the case of first cage the total no. of marble buried was found to be 07, in second one it was 8 and in the case of third, fourth, fifth, sixth, seven, eight, nine, ten, eleven and twelve cage it was found to be 04, 03, 07, 06, 07, 05, 07, 02, 06 and 03 respectively. The results indicate that the highest number of marble buried was found to be in the cage number second.

Table 5: Effect of agomelatine (50 mg/kg, i.p.) on marble burying behavior

S. No.	Cage No.	Wt. of mice (g)	No. of male mice	Time spend in cage (min.)	No. of marble buried
1	I	21.73	01	30	07
2	II	20.64	01	30	08
3	III	23.01	01	30	04
4	IV	22.98	01	30	03
5	V	23.92	01	30	07
6	VI	20.56	01	30	06
7	VII	22.98	01	30	07
8	VIII	20.63	01	30	05
9	IX	21.27	01	30	07
10	X	22.34	01	30	02
11	XI	20.78	01	30	06
12	XII	21.92	01	30	03

CONCLUSION

On studying the comparative study of agomelatine on the rodents, pre treated with pCPA (Selective serotonin depletor), agomelatine shows the less no. of locomotor count and marble buried count, which indicate the decrement in stress and anxiety level which is related to OCD. In the present work agomelatine a novel melatonergic analogue dose-dependently attenuated marble-burying behavior in mice. In addition, this effect of agomelatine was maintained after its administration for 10 days.

It is observed that mice do not avoid marbles when given the opportunity to do so, indicating their non-aversive property. In addition, repeated exposure to marbles does not induce habituation, suggesting that this behaviour is not related to novelty or fear however, because the marbles are nonreactive, they cannot provide the animal with the necessary stimuli to a natural ending of the investigation, and this 'frustrated' investigation leads to compulsive burying. Hence, although inhibition of object burying was originally suggested as a screening test for anxiolytic activity, the above findings and the reduction in burying behavior by serotonin reuptake inhibitors suggest that this behavior may be related to obsessive-compulsive disorder. For these reasons, we selected marble-burying behavior as a paradigm to screen the anticomulsive effect of agomelatine. It is still a matter of debate whether marble burying measures anxiety or compulsivity; however, it is clear that marble burying is decreased by both anxiolytic drugs and anticomulsive drugs. Therefore, our results suggest that agomelatine may have anti-anxiety or anti-compulsive activity.

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