

EFFECT OF AGOMELATINE IN THE TREATMENT OF OBSESSIVE COMPULSIVE DISORDER USING MARBLE-BURYING BEHAVIOR

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ABSTRACT

Agomelatine, a melatonergic analogue drug, which potently activates human melatonin 1 (MT₁) and MT₂ receptors and selectively antagonizes the action of serotonin at 5HT_{2c} receptor, was recently approved for the treatment of major depression. In the present work, a randomized, double-blind, placebo-controlled trial was performed to check the efficacy of agomelatine in treatment of anxiety disorder, prompting its therapeutic potential in treatment of obsessive-compulsive disorder (OCD). 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. In addition, to rule out the role of enhanced serotonergic neurotransmission, studies were carried out in *p*-chlorophenylamine (PCPA). 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: Agomelatine, Obsessive compulsive disorder (OCD), Marble-burying behavior (MBB), Melatonin.

INTRODUCTION

Agomelatine is a new melatonin analogue drug recently approved for treatment of major depression in adults including prevention of relapse. Agomelatine exhibits a new pharmacological mechanism of action, which combines its melatonin MT₁ receptor and MT₂ receptor agonist properties with a serotonin (5-HT) 2C receptor antagonist effect. Owing to this novel mechanism of action there is a widespread excitement about its therapeutic potential in treatment of variety of central nervous system disorders.

Obsessive compulsive disorder (OCD) is characterized by persistent thoughts (obsessions), which are ego-dystonic and associated with seemingly purposeful behaviors (compulsions). In addition, it is also classified as

a generalized anxiety disorder. Only potent serotonin reuptake inhibitors are consistently effective in patients with obsessive compulsive disorder. The pathophysiology of OCD is associated with dysregulation in the serotonergic system and hyperactivity of dopamine. Abnormal glutamatergic neurotransmissions were observed in the caudate nuclei of OCD patients and the literature suggests that there are elevated CSF CRF concentrations in patients with obsessive-compulsive disorder.

The pharmacodynamic profile of agomelatine and its efficacy in variety of CNS disorders prompted us to evaluate its effect on compulsive behavior. Agents with potential for increasing central serotonergic transmission are consistently found to reduce the marble-burying

behavior. Hence, to rule out participation of any such effect in agomelatine's action, separate studies were carried out in *p*-chlorophenylalanine treated mice

MATERIAL AND METHODS

The Adult male albino Swiss mice (22-25 g) were group housed [mice (n=6)] under a standard 12 h light/dark cycle and controlled conditions of temperature and humidity (25±2°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.

Drugs

Agomelatine and DL-4-chloro-phenylalanine (PCPA a selective serotonin depletor) were purchased from Sigma-Aldrich, MO, USA. Venlafaxine was gifted by Sun Pharmaceuticals, Baroda, India. Diazepam injection (Anxol) were purchased from SVIZERA Health Care Ltd., melatonin was procured from Aristo Pharma, Bhopal.

Volume of drug administration

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

APPARATUS

Marble-burying behavior test apparatus

It consisted of plastic cages (40 × 28 × 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).

Assessment of marble-burying behavior in mice

The marble-burying behavior of mice was recorded 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.

TREATMENTS

Experiment 1: Acute study

Mice were randomly assigned to treatment conditions (n=6/12) in which Agomelatine (10, 50mg/kg,i.p.), Melatonin(5,10,15,20 mg/kg.i.p.) were administered. Marble-burying behavior was tested for 30 min after the administration of drugs.

Experiment 2: Chronic study

Mice were randomly assigned to treatment conditions (n=6/12) in which agomelatine (20, 30 mg/kg,i.p.), melatonin (15 mg/kg,i.p.) were administered for 10 days. Marble-burying behavior was tested on day 11, 30 min after the last treatment.

Experiment 3: Combined drug study

➤ Mice were randomly assigned to treatment conditions (n=6/12) in which:

➤ Pre-treated with PCPA (300 mg/kg, i.p.) for 3 consecutive days and 24 hr thereafter 0.9% saline (10 ml/kg, i.p.) was administered 30 min prior to testing.

➤ Pre-treated with PCPA (300 mg/kg, i.p.) for 3 consecutive days, and 24 hr thereafter agomelatine (20, 30 mg/kg, i.p.) was administered 30 min prior to testing.

Each treatment had its respective control group, which received respective vehicle treatment by respective route.

Statistical analysis

Data from experiment 1 were analyzed by one-way analysis of variance (ANOVA), followed by Dunnett's test for multiple comparisons; data from experiment no. 2 were analyzed by one-way analysis of variance (ANOVA), followed by Tukey's test for multiple comparisons; and data from experiment 3 were analyzed with two-way ANOVA, followed by Bonferroni's multiple comparisons test. The results are expressed as mean±SD of 6-12 observations. *P* value less than 0.05 was considered to be statistically significant.

RESULTS

Experiment 1: Acute study

Influence of acute drug treatment on MBB

(a) Agomelatine

One-way ANOVA revealed that acute administration of Agomelatine in different doses had a significant effect on the MBB of male mice [$F(5,53)=6.835, P<0.0001$].

Post hoc analysis

Further the dunnett multiple comparison test revealed that agomelatine had a significant effect at 20mg/Kg ($P<0.01$), 30mg/Kg ($P<0.05$) and at 50mg/kg ($P<0.001$) however the lower dose found to be non-significant at 10mg/Kg($P>0.05$).

(b) Melatonin

One-way ANOVA revealed that acute administration of Melatonin in different doses had a significant effect on the MBB of male mice [$F(4,31)=5.427, P<0.0024$].

Post hoc analysis

Further the dunnett multiple comparison test revealed that melatonin had a significant effect at 15

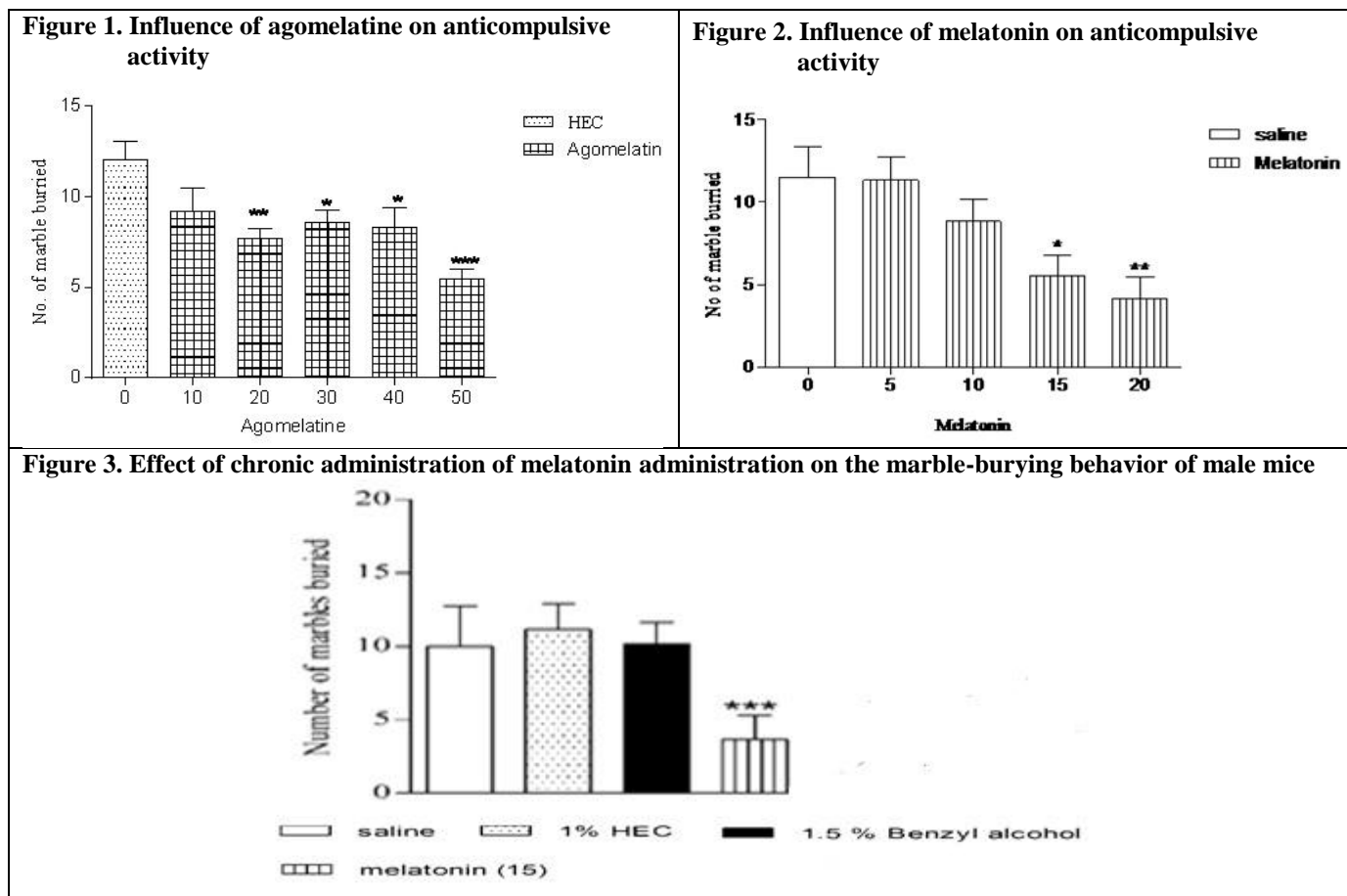
mg/Kg ($P < 0.05$) and 20mg/Kg ($P < 0.01$) however the lower dose found to be non-significant at 5 and 10mg/Kg ($P > 0.05$).

Experiment 2: Chronic study

Influence of chronic drug treatment on MBB

Effect of various chronic drug treatments on the marble-burying behavior of mice is depicted in Fig. 3.

One-way ANOVA indicated a significant influence of all drug treatments on the marble-burying behavior of mice [$F(7, 47) = 20.25$; $P < 0.0001$]. Tukey's post-hoc test indicated that chronic administration of melatonin (15 mg/kg), venlafaxin (5 mg/kg), diazepam (0.5 mg/kg), and agomelatine (20, 30 mg/kg) significantly ($P < 0.001$) inhibited the marble-burying behavior.



CONCLUSION

In conclusion, the result of the present investigation support a potential strength of melatonergic drugs, melatonin and agomelatine on compulsive behavior

in mice. Further this effect appears to be due to modulation of melatonergic receptors and not due to serotonergic system.

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