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# Memory facilitating effects of agomelatine in the novel object recognition memory paradigm in the rat

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ABSTRACT

The aim of the present study was to evaluate the effects of agomelatine, an antidepressant with melatonergic agonist and 5-$HT_{2C}$ antagonist properties, in the rat novel object recognition (NOR) task, a model of short-term episodic memory. To assess the potential involvement of its chronobiotic activity, single intraperitoneal administration of agomelatine and NOR testing were performed either in the evening or in the morning. In both conditions, using a 24 h retention interval, vehicle-treated rats did not discriminate between the novel and the familiar object (recognition index was not different from chance performance) while object memory performance of rats treated with agomelatine either in the evening (10 and 40 mg/kg) or in the morning (2.5, 10, and 40 mg/kg) was significantly improved. Moreover, the selective 5-$HT_{2C}$ antagonist SB 242,084 (0.63, 2.5, and 10 mg/kg) and melatonin (2.5, 10, and 40 mg/kg) displayed also memory facilitating effects in both administration conditions. Finally, thioperamide used as positive reference compound to validate the experimental conditions, demonstrated a memory facilitating effect. In conclusion, agomelatine was shown to possess memory facilitating effects in the rat NOR task and both melatonergic agonist and 5-$HT_{2C}$ antagonist properties could be involved in these effects.



## 1. Introduction

Agomelatine is a novel antidepressant acting as a potent agonist of melatonergic MT1 and MT2 receptors (Ying et al., 1996; Yous et al., 1992) and an antagonist of the 5-$HT_{2C}$ receptors (Millan et al., 2003). Agomelatine has demonstrated a clear efficacy as an antidepressant in clinical trials (Kennedy and Emsey, 2006; Lôo et al., 2002; Olie and Kasper, 2007; Kennedy, 2009; Kennedy and Rizvi, 2010) with fewer side-effects than more classical antidepressants (Kasper and Hamon, 2009; Kennedy and Rizvi, 2010).

The chronobiotic activity of agomelatine may contribute to its efficacy in treating patients with major depressive disorder (MDD), the disruption of internal circadian rhythms being one important feature of depression (Wehr and Wirz-Justice, 1982). Indeed, in preclinical studies, agomelatine is able to re-synchronise disrupted circadian rhythms (Armstrong et al., 1993; Martinet et al., 1996; Redman et al., 1995; Van Reeth et al., 1997). After chronic treatment, agomelatine dose-dependently restored the phase shifting response to a dark pulse (Van Reeth et al., 2001) and accelerated the resynchronization of the rhythm to new light–dark cycle in aged hamsters by 25% (Weibel et al., 2000). The re-entraining activity of agomelatine is linked to its receptor profile, and a clear relation between plasma agomelatine concentration and entrainment has been demonstrated (Martinet et al., 1996).

In preclinical studies, agomelatine has been shown to display antidepressant and anxiolytic properties in different experimental models: antidepressant-like effects of agomelatine have been shown in the forced swimming test (Bourin et al., 2004), the chronic mild stress model (Papp et al., 2003), the learned helplessness model (Bertaina-Anglade et al., 2006a) and a transgenic mouse model with low glucocorticoid receptor function (Barden et al., 2005); anxiolytic-like effects of agomelatine have been described in rats subjected to the social interaction test and the Vogel conflict procedure (Millan et al., 2005), the elevated plus-maze test (Papp et al., 2006) and the social defeat model (Tuma et al., 2005).

Preclinical (Henningsen et al., 2009; Kalueff and Murphy, 2007) and clinical (Baune et al., 2008; Hammar and Ardal, 2009) data suggest that depressive disorders are often associated with cognitive impairment in different cognitive domains such as executive function, working memory and attention. In order to evaluate the effects of agomelatine on memory, we initially tested the compound in a reference memory model, the T maze left–right spatial discrimination test. In this model, a single administration of agomelatine (1 and 10 mg/kg) improved discrimination performance of the mice, the effect being more intense when agomelatine was administered in the evening compared to a morning administration (Jaffard et al., 1993). Besides, recent data suggests that, following chronic treatment, agomelatine (10 mg/kg) is able to reverse a stress-induced spatial

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memory impairment in the rat assessed in the radial-arm water maze (Conboy et al., 2009).

In the present study, the effects of agomelatine were assessed in the novel object recognition (NOR) task, a simple non-rewarded recognition memory test (Ennaceur and Delacour, 1988). The NOR task is being increasingly used as an experimental tool in assessing drug effects on memory and can also be used in safety pharmacology to identify pro-amnesic properties of new drugs (Bertaina-Anglade et al., 2006b). This paradigm is sensitive to pharmacological manipulations e.g. phencyclidine (PCP) challenge (Grayson et al., 2007) or cholinergic hypofunction (Bartolini et al., 1996) and to ageing (Platano et al., 2008; Scali et al., 1997). This task is based on the natural propensity of rats to explore novelty in their environment (Dere et al., 2007).

More specifically, rodents are able to discriminate between a novel and a previously seen (i.e. familiar) object. During the first (learning) trial, rats are exposed to two identical objects. Then, after an inter-trial interval (ITI), one of the previously explored objects now familiar is introduced during a test trial, together with a novel object. At short ITIs, rats can discriminate between the two objects, spending more time exploring the novel object than the familiar one. NOR is sensitive to delay intervals (Ennaceur and Delacour, 1988; Ennaceur and Meliani, 1992; Pitsikas and Sakellaridis, 2005). With longer ITI (24 h), animals are unable to discriminate between the familiar and a novel object, spending the same amount of time with the two objects. This situation of forgetting is exploited to screen for memory facilitating drugs.

The NOR test has been widely used as a pre-clinical test to investigate the memory enhancing effects of acetylcholinesterase inhibitors such as donepezil (Prickaerts et al., 2005) and galantamine (de Bruin and Pouzet, 2006) used as treatments in Alzheimer's disease. Besides, histamine $H_3$ receptor antagonists have been demonstrated to improve learning and memory in various experimental models in rodents likely via an increase of the central histaminergic tone and histaminergic–cholinergic interactions (see Giovannini et al., 1999; Vohora, 2004). In the NOR task, thioperamide, "prototype" of the histamine $H_3$ receptor antagonists, improved long-term (24 h) object recognition memory (Giovannini et al., 1999; Orsetti et al., 2001). Thus, thioperamide was chosen as reference compound to validate the NOR experimental conditions used in this study.

Presently, as regards the mechanistic profile of action of agomelatine, the effects of a single administration of agomelatine in the NOR model were compared to those of a similar treatment with melatonin and a selective 5-$HT_{2C}$ receptor antagonist (SB 242,084). Furthermore, administration of the compounds was performed at two different moments across the daily cycle. Indeed, significant diurnal variations of melatonin receptor agonist activity have been reported for melatonin on exploration and anxiety (Golombek et al., 1993). Accordingly, agomelatine displays a chronobiotic activity after an evening treatment but is devoid of any chronobiotic effect after a morning administration (Van Reeth et al., 1997). Thus, in the present NOR test, the effects of agomelatine, melatonin and SB 242,084 were assessed in the evening (within 2 h before the beginning of the dark phase of the 12-h light/dark cycle) and in the morning (within 3 h after the end of the dark phase).

Thus, the present study was designed to assess 1) the effects of agomelatine in the NOR paradigm and 2) if agomelatine is shown to be effective in the test, the participation of its melatonergic agonist and 5-$HT_{2C}$ antagonist properties to these effects and the potential link with its chronobiotic activity.

## 2. Materials and methods

### 2.1. Animals

Experiments were carried out using male Sprague–Dawley rats (Centre d'élevage Janvier, France, n = 12–15 per group) weighing 220–300 g (6 weeks old). The animals were housed 2 to 4 individuals per cage, in a regulated environment (22 ± 2 °C, 55 ± 10% relative humidity, 12–12 h light/dark cycle, light on at 6:00 am in experiments 1 and 2 and at 8:00 am in experiment 3) with free access to food and water. The acclimation period before the beginning of the experiments was 5 days.

After testing was completed, rats were sacrificed according to ethical guidelines. All used animal procedures are in compliance with international European ethical standards (86/609-EEC) and with the French National Committee (decret 87/848) for the care and use of laboratory animals.

### 2.2. Novel object recognition task

The novel object recognition (NOR) task adapted from Bartolini et al. (1996) was performed in a square wooden open-field apparatus (60 × 60 × 40 cm) with black painted squares (15 × 15 cm) under a clear plexiglass floor. The open-field was placed in a room illuminated only by a halogen lamp orientated towards the ceiling and giving a uniform dim light in the apparatus (intensity of 60 lx). The open-field (floor and walls) and the objects were washed with water and dried thoroughly after each trial. The objects were different in shape, colour and texture. They were made of stone, painted wood, glass and plastic, around 15 cm high and were too heavy to be displaced by rats. Triplicate copies of each object were obtained and each pair of objects was previously tested for absence of spontaneous preference for one member of the pair (unpublished observations). In each experimental group, the role (familiar versus novel object) as well as the relative position of the two objects was counterbalanced and randomly permuted. Rats were placed in the experimental room for at least 30 min before testing.

The day prior to the test, rats received a single habituation session to the open-field. They were allowed to explore freely the test apparatus in the presence of 2 objects for a 3-min period.

Rats were submitted to two trials with a 24 hour intertrial interval (ITI). During the first trial (learning trial, $T_1$), animals were placed in the open-field containing 2 identical objects for the amount of time necessary to spend a total of 15 s exploring these 2 objects. Any rat not exploring the objects for 15 s within a cut-off time of 4 min was excluded from the experiments. Exploration was defined as the animal having its head within 2 cm of the object while looking at, sniffing, or touching it. In the second trial (test trial, $T_2$) which lasted 3 min, animals were exposed to an identical copy of the objects previously seen during the first trial and a novel object. Animals with low level of object exploration (novel + familiar < 5 s) were excluded from the data analysis. During each trial, locomotor activity was scored as the number of lines crossed per minute.

Scoring was performed by experimenters unaware of the pharmacological treatment and of the value (novel or familiar) of each object.

### 2.3. Drugs

Agomelatine (S 20098) and hydroxyethylcellulose (HEC) were provided by the Institut de Recherches Internationales Servier (France). Melatonin and SB 242,084 (6-chloro-5-methyl-1-[2-(2-methylpyridyl-3-oxy)-pyrid-5-yl carbamoyl] indoline), a selective 5-$HT_{2C}$ receptor antagonist (Kennett et al., 1997; Martin et al., 2002; Mosher et al., 2005) were purchased from Sigma-Aldrich. Thioperamide maleate was purchased from Biotrend. Agomelatine and melatonin were tested at doses of 2.5, 10 and 40 mg/kg and SB 242,084 at doses of 0.63, 2.5 and 10 mg/kg. The dose of 0.5 mg/kg of thioperamide was chosen as the most efficient dose in the present experimental conditions (Biotrial, unpublished observations). All drugs were reconstituted in a suspension with the vehicle HEC 1% (w/v) in distilled water. Animals were administered intraperitoneally (i.p.) in a volume of 5 ml/kg body weight.

### 2.4. Drug administration schedule

#### 2.4.1. Experiments 1 and 2: Evening administration

In these experiments, NOR testing was performed between 4:00 pm and 6:00 pm on two consecutive days. So, both the learning trial and the test trial 24 h later, were performed during the last 2 h of light (light off at 6:00 pm). Agomelatine, melatonin and SB 242,084 were administered 30 min before the test trial. Thioperamide was administered 40 min before the test trial.

#### 2.4.2. Experiment 3: Morning administration

In this experiment, NOR testing was performed between 8:00 am and 11:00 am on two consecutive days. Both the learning trial and the test trial 24 h later, were performed during the first 3 h of light (light on at 8:00 am). As in experiments 1 and 2, agomelatine, melatonin and SB 242,084 were administered 30 min before the test trial and thioperamide 40 min before the test trial.

Experiments were performed across several 2-day NOR testing. In each of them, animals were tested in subgroups of 16 (with a 7-min time interval between 2 rats for $T_1$ and $T_2$) allowing to have all treatment groups represented in each 2-day NOR testing.

### 2.5. Statistical analysis

Object exploration was characterised by the following parameters: time (s) required to achieve 15 s of object exploration during $T_1$ (duration of $T_1$), time (s) spent in active exploration of the familiar (F) or novel (N) object during $T_2$, and total time (s) spent exploring both objects during $T_2$. Recognition memory was evaluated using a recognition index (RI) calculated for each animal using the formula: $(N-F/N+F)\times 100$ corresponding to the difference between the time exploring the novel and the familiar object, corrected for the total time spent exploring both objects during $T_2$, this ratio allows for adjustments to any differences in total exploration time (Ennaceur, 1998; Ennaceur and Delacour, 1988; Pitsikas and Sakellaridis, 2005). Locomotor activity was assessed by calculating the number of lines crossed per minute during $T_1$ and during $T_2$. Results are expressed as mean ± S.E.M. In each experiment and for each treatment, the duration of $T_1$, the total time spent exploring both objects during $T_2$ and the locomotor activity during $T_1$ and during $T_2$ were analysed using a one-way analysis of variance (ANOVA), followed by a Dunnett's test. RI data was analysed using a two-sided Student's t test for paired samples to compare the recognition index to chance performance (when RI = 0%).

## 3. Results

### 3.1. Learning phase: Duration of the learning trial

In each experiment, statistical analyses performed on the duration of the learning trial showed no significant difference between-groups (Table 1). These results suggest that animals have been correctly randomised across groups in the different experiments.

**Table 1**
Duration of the learning trial.

| | n | Duration of $T_1$ (s) |
|---|---|---|
| *First experiment (evening)* | | |
| Vehicle | 13 | 161.8 ± 10.0 |
| Agomelatine 2.5 mg/kg | 13 | 163.5 ± 9.4 |
| Agomelatine 10 mg/kg | 13 | 147.8 ± 12.4 |
| Agomelatine 40 mg/kg | 13 | 156.5 ± 11.2 |
| SB 242,084 0.63 mg/kg | 12 | 163.3 ± 12.4 |
| SB 242,084 2.5 mg/kg | 12 | 156.7 ± 13.8 |
| SB 242,084 10 mg/kg | 12 | 170.8 ± 14.4 |
| Thioperamide 0.5 mg/kg | 15 | 156.5 ± 12.1 |
| *Second experiment (evening)* | | |
| Vehicle | 12 | 171.8 ± 12.4 |
| Agomelatine 2.5 mg/kg | 13 | 168.2 ± 14.9 |
| Agomelatine 10 mg/kg | 13 | 168.0 ± 16.6 |
| Agomelatine 40 mg/kg | 12 | 166.3 ± 12.8 |
| Melatonin 2.5 mg/kg | 13 | 161.2 ± 12.3 |
| Melatonin 10 mg/kg | 13 | 177.2 ± 9.6 |
| Melatonin 40 mg/kg | 12 | 173.1 ± 8.6 |
| Thioperamide 0.5 mg/kg | 12 | 159.8 ± 12.7 |
| *Third experiment (morning)* | | |
| Vehicle | 12 | 160.7 ± 10.1 |
| Agomelatine 2.5 mg/kg | 12 | 162.3 ± 11.0 |
| Agomelatine 10 mg/kg | 12 | 163.4 ± 14.9 |
| Agomelatine 40 mg/kg | 13 | 164.2 ± 11.7 |
| SB 242,084 0.63 mg/kg | 14 | 162.2 ± 13.4 |
| SB 242,084 2.5 mg/kg | 12 | 160.3 ± 15.7 |
| SB 242,084 10 mg/kg | 12 | 160.0 ± 12.0 |
| Melatonin 2.5 mg/kg | 13 | 166.1 ± 14.8 |
| Melatonin 10 mg/kg | 12 | 159.7 ± 14.0 |
| Melatonin 40 mg/kg | 12 | 161.0 ± 18.0 |
| Thioperamide 0.5 mg/kg | 12 | 162.9 ± 12.3 |

Data expressed as mean ± S.E.M. n = number of animals included per group. Duration of $T_1$ (s) = total time spent in the open-field to reach the 15-s exploration criterion during $T_1$.

### 3.2. Experiment 1: Effects of agomelatine and SB 242,084 in the NOR task with evening administration

The comparison of the recognition index to chance performance showed that RI of rats treated with agomelatine at 10 and 40 mg/kg (RI = 28 ± 6% and 23 ± 4%, respectively) or with SB 242,084 at 0.63, 2.5 and 10 mg/kg (RI = 24 ± 7%, 17 ± 4% and 20 ± 6%, respectively) was significantly different from chance performance (with $p<0.05$). In contrast, RI of rats treated with agomelatine at 2.5 mg/kg (RI = 13 ± 7%) and treated with vehicle (RI = 2±8%) was not significantly different from chance performance. In addition, RI of thioperamide-treated rats (RI = 29 ± 6%) was significantly different from chance performance (with $p<0.05$) (Fig. 1).

The analysis of variance showed significant effects of agomelatine treatment on locomotor activity (Table 2) during the learning trial [$F(3,51)=3.62$; $P<0.05$] and the test trial [$F(3,51)=4.04$; $p<0.05$]. Locomotor activity of rats treated with agomelatine at 10 mg/kg was significantly increased during $T_1$ (37.0 ± 1.8 crossed lines/min) and $T_2$ (32.7 ± 1.8 crossed lines/min) when compared to their respective controls (30.9 ± 1.8 and 25.2 ± 1.7 crossed lines/min; with $p<0.05$ for both comparisons). In addition, a significant effect of SB 242,084 treatment was observed during $T_2$ [$F(3,48)=6.69$; $p<0.05$], with locomotor activity significantly increased at the 3 tested doses (34.1 ± 1.0, 35.2 ± 1.5 and 32.8 ± 2.6 crossed lines/min for 0.63, 2.5 and 10 mg/kg, respectively) compared to vehicle treatment (with $p<0.05$). Thioperamide had no effect on locomotor activity. No statistically significant effects were observed on the total time spent exploring the objects during $T_2$ whatever the treatment (see Table 2). Overall, the inclusion rate of the animals in this experiment was between 80 and 87% (data not shown).

### 3.3. Experiment 2: Effects of agomelatine and melatonin in the NOR task with evening administration

Analysis of the recognition index showed that RI of groups treated with agomelatine at 2.5, 10 and 40 mg/kg (RI = 33 ± 6%, 24 ± 6% and 25 ± 10%, respectively) along with RI of groups treated with melatonin at 2.5 and 10 mg/kg (RI = 21 ± 5% and 20 ± 7%, respectively) was significantly different from chance performance (with $p<0.05$). In contrast, RI of group treated with melatonin at 40 mg/kg (RI = 9 ± 14%) and vehicle group (RI = 9 ± 6%) was not significantly different from chance performance. In addition, RI of rats treated with thioperamide at 0.5 mg/kg (RI = 38 ± 6%) was significantly different from chance performance (with $p<0.05$) (Fig. 2).

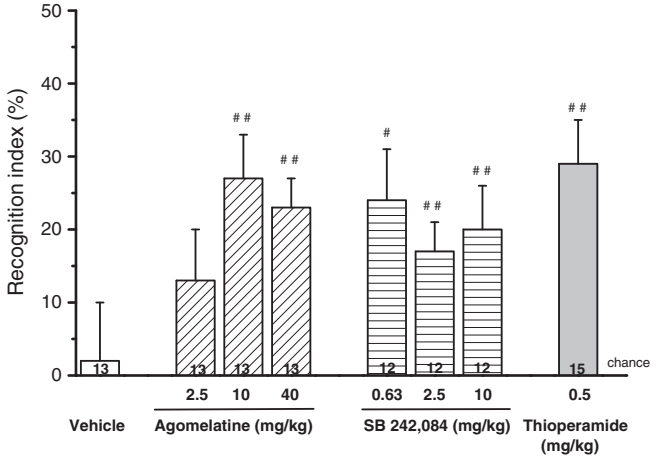


**Fig. 1.** Effects of a single intraperitoneal administration of agomelatine and SB 242,084 on memory performance (expressed as recognition index) in the NOR task. Administration and NOR task were performed in the evening (see Materials and methods for details). Comparison with thioperamide used as positive reference compound. Results are expressed as mean ± S.E.M. Number of rats per group is indicated in the corresponding histograms. $^{\#}p<0.05$ and $^{\#\#}p<0.01$ versus chance performance (Student's t test).

The analysis of variance showed significant effects of agomelatine treatment on locomotor activity (Table 2) during the test trial [$F(3,49)=2.85$; $p<0.05$]. As observed for experiment 1, locomotor activity of rats treated with agomelatine at 10 mg/kg was significantly increased during $T_2$ (33.7 ± 1.6 crossed lines/min) when compared to vehicle-treated rats (27.1 ± 1.1 crossed lines/min; with $p<0.05$). Melatonin and thioperamide treatments had no significant effect on locomotor activity. No statistically significant effects of agomelatine, melatonin or thioperamide treatments were observed on the total time spent exploring the objects during $T_2$ (see Table 2). Overall, the inclusion rate of the animals in this experiment was between 75 and 87% (data not shown).

### 3.4. Experiment 3: Effects of agomelatine, melatonin and SB 242,084 in the NOR task with morning administration

Analysis of the RI showed that rats treated with agomelatine at 2.5, 10 and 40 mg/kg (RI = 17 ± 5%, 36 ± 7% and 28 ± 6%, respectively), with SB 242,084 at 0.63, 2.5 and 10 mg/kg (RI = 34 ± 5%, 35 ± 6% and 20 ± 5%, respectively) and with melatonin at 2.5, 10 and 40 mg/kg (RI = 20 ± 7%, 29 ± 7% and 21 ± 7%, respectively) displayed RI significantly different from chance performance (with $p<0.05$). In contrast, memory performance of rats vehicle-treated (RI = 2 ± 6%) was not significantly different from chance performance. In addition, RI of rats treated with thioperamide at 0.5 mg/kg (RI = 37 ± 8%) was significantly different from chance performance (with $p<0.05$) (Fig. 3).

The analysis of variance showed significant effects of SB 242,084 treatment on locomotor activity (Table 2) during $T_2$ [$F(3,48)=3.67$; $p<0.05$]. Locomotor activity of rats treated with SB 242,084 at 0.63, 2.5 and 10 mg/kg was significantly increased during $T_2$ (34.2 ± 1.9, 36.1 ± 1.9 and 34.4 ± 2.3 crossed lines/min, respectively) when compared to vehicle-treated rats (27.5 ± 1.5 crossed lines/min; with $p<0.05$ for all comparisons). Agomelatine, melatonin and thioperamide treatments did not significantly affect locomotor activity or total time spent exploring the objects during $T_2$ (see Table 2). Overall, the inclusion rate of the animals in this experiment was between 75 and 81% (data not shown).

**Table 2**
Locomotor activity during learning and test trials — object exploration during test trial.

| | n | Locomotor activity (crossed lines/min) | | Object exploration(s) |
|---|---|---|---|---|
| | | $T_1$ | $T_2$ | $T_2$ |
| *First experiment (evening)* | | | | |
| Vehicle | 13 | 30.9 ± 1.8 | 25.2 ± 1.7 | 15.8 ± 2.6 |
| Agomelatine 2.5 mg/kg | 13 | 29.9 ± 1.5 | 26.3 ± 1.5 | 20.8 ± 2.5 |
| Agomelatine 10 mg/kg | 13 | 37.0 ± 1.8$^{\#}$ | 32.7 ± 1.8$^{*}$ | 20.3 ± 1.7 |
| Agomelatine 40 mg/kg | 13 | 34.2 ± 1.8 | 30.4 ± 2.0 | 17.3 ± 2.4 |
| SB 242,084 0.63 mg/kg | 12 | 33.3 ± 1.3 | 34.1 ± 1.0$^{**}$ | 16.5 ± 1.9 |
| SB 242,084 2.5 mg/kg | 12 | 34.5 ± 1.9 | 35.2 ± 1.5$^{***}$ | 14.8 ± 1.8 |
| SB 242,084 10 mg/kg | 12 | 31.2 ± 2.8 | 32.8 ± 2.6$^{*}$ | 16.3 ± 2.5 |
| Thioperamide 0.5 mg/kg | 15 | 34.6 ± 1.5 | 28.0 ± 1.0 | 18.5 ± 1.8 |
| *Second experiment (evening)* | | | | |
| Vehicle | 12 | 30.5 ± 1.5 | 27.1 ± 1.1 | 16.3 ± 2.5 |
| Agomelatine 2.5 mg/kg | 13 | 29.5 ± 2.4 | 28.2 ± 1.9 | 19.0 ± 2.0 |
| Agomelatine 10 mg/kg | 13 | 36.1 ± 2.0 | 33.7 ± 1.6$^{*}$ | 17.8 ± 1.8 |
| Agomelatine 40 mg/kg | 12 | 34.7 ± 1.7 | 31.7 ± 2.4 | 19.8 ± 1.6 |
| Melatonin 2.5 mg/kg | 13 | 35.0 ± 1.3 | 31.9 ± 1.4 | 20.2 ± 2.0 |
| Melatonin 10 mg/kg | 13 | 32.2 ± 2.0 | 30.4 ± 2.4 | 19.8 ± 1.9 |
| Melatonin 40 mg/kg | 12 | 33.2 ± 2.5 | 28.7 ± 3.0 | 11.1 ± 1.8 |
| Thioperamide 0.5 mg/kg | 12 | 31.5 ± 1.0 | 29.9 ± 2.3 | 21.0 ± 2.1 |
| *Third experiment (morning)* | | | | |
| Vehicle | 12 | 30.7 ± 1.8 | 27.5 ± 1.5 | 22.2 ± 2.9 |
| Agomelatine 2.5 mg/kg | 12 | 32.3 ± 2.2 | 31.8 ± 1.2 | 18.8 ± 1.3 |
| Agomelatine 10 mg/kg | 12 | 32.3 ± 2.1 | 32.4 ± 2.4 | 17.6 ± 1.8 |
| Agomelatine 40 mg/kg | 13 | 28.4 ± 1.8 | 27.7 ± 1.7 | 17.7 ± 2.0 |
| SB 242,084 0.63 mg/kg | 14 | 31.4 ± 1.7 | 34.2 ± 1.9$^{*}$ | 16.1 ± 1.1 |
| SB 242,084 2.5 mg/kg | 12 | 35.5 ± 2.7 | 36.1 ± 1.9$^{*}$ | 20.3 ± 1.8 |
| SB 242,084 10 mg/kg | 12 | 32.2 ± 1.9 | 34.4 ± 2.3$^{*}$ | 15.8 ± 1.1 |
| Melatonin 2.5 mg/kg | 13 | 31.3 ± 1.9 | 27.9 ± 1.7 | 20.8 ± 1.3 |
| Melatonin 10 mg/kg | 12 | 30.6 ± 2.1 | 27.8 ± 2.0 | 21.9 ± 2.4 |
| Melatonin 40 mg/kg | 12 | 33.1 ± 2.5 | 30.4 ± 2.3 | 17.0 ± 2.1 |
| Thioperamide 0.5 mg/kg | 12 | 33.8 ± 2.2 | 29.1 ± 1.3 | 18.3 ± 1.8 |

Data are expressed as mean ± S.E.M. n = number of animals per group. $^{\#}p<0.05$ versus vehicle group during $T_1$. $^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$ versus vehicle group during $T_2$. Object exploration (s) = total time spent exploring both objects during $T_2$.

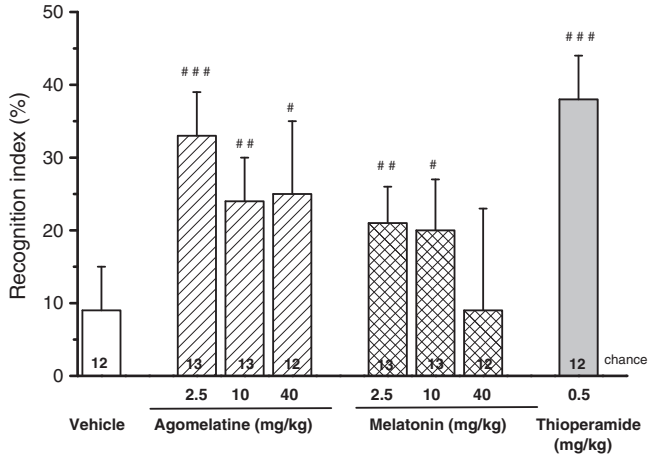


**Fig. 2.** Effects of a single intraperitoneal administration of agomelatine and melatonin on memory performance (expressed as recognition index) in the NOR task. Administration and NOR task were performed in the evening (see Materials and methods for details). Comparison with thioperamide used as positive reference compound. Results are expressed as mean ± S.E.M. Number of rats per group is indicated in the corresponding histograms. $^{\#}p<0.05$, $^{\#\#}p<0.01$ and $^{\#\#\#}p<0.001$ versus chance performance (Student's t test).

## 4. Discussion

The present study demonstrates that agomelatine (2.5, 10 and 40 mg/kg), melatonin (2.5, 10 and 40 mg/kg) and SB 242,084 (0.63, 2.5 and 10 mg/kg) following a single morning or evening i.p. administration, can enhance object recognition memory with a 24 h retention delay, a situation in which memory performance is reduced in control rats. In order to validate our experimental conditions, the histamine $H_3$ receptor antagonist thioperamide was used as a reference compound. In the present NOR test and as previously described (Giovannini et al., 1999; Orsetti et al., 2001), thioperamide improved object recognition memory, validating the test.

In the present study, the locomotor activity should not be a confounding factor for the evaluation of memory performance of the animals. Indeed, the motor stimulant effects observed after evening administration of agomelatine (10 mg/kg) and after morning and evening administration of SB 242,084 did not affect the exploration of the objects during the test trial. Furthermore, the anxiolytic activity of the study compounds (Millan et al., 2005; Papp et al., 2006; Tuma et al., 2005; Kantor et al., 2005) should not be involved in the present memory facilitating effects, as the NOR test requires little training of animals and does not induce high levels of stress and arousal (Dere et al., 2007). Globally, the involvement of non-cognitive components, such as motor stimulant effects or anxiolytic activity, in the memory facilitating effects of the tested compounds seems to be unlikely.

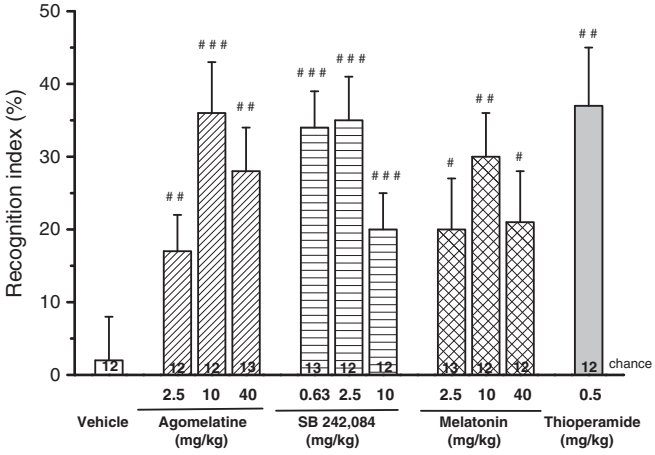


**Fig. 3.** Effects of single intraperitoneal administration of agomelatine, SB 242,084 and melatonin on memory performance (expressed as recognition index) in the NOR task. Administration and NOR task were performed in the morning (see Materials and methods for details). Comparison with thioperamide used as positive reference compound. Results are expressed as mean ± S.E.M. Number of rats per group is indicated in the corresponding histograms. $^{\#}p<0.05$, $^{\#\#}p<0.01$ and $^{\#\#\#}p<0.001$ versus chance performance (Student's t test).

The effects of agomelatine on recognition memory were compared to those of the selective 5-$HT_{2C}$ receptor antagonist SB 242,084. The present results show a memory facilitating effects of SB 242,084 (0.63, 2.5 and 10 mg/kg) for both morning and evening administration. At low doses (up to 1 mg/kg i.p.) and using electroencephalogram recordings, SB 242,084 has been previously reported to increase rat's neocortical θ activity during wakefulness without affecting vigilance states, raising the possibility of a memory facilitating effect of the drug (Kantor et al., 2005). Furthermore, it was previously shown that a systemic administration of the 5-$HT_{2C}$ receptor antagonist RO 60-0491 (3 mg/kg i.p.) was able to facilitate the object recognition memory at a 24 h retention delay (Pitsikas and Sakellaridis, 2005), suggesting that blockade of the 5-$HT_{2C}$ receptors may be important for recognition memory. By blocking the 5-$HT_{2C}$ receptors, agomelatine induces a frontocortical release of dopamine in the rat brain (Millan et al., 2003). There is some evidence to suggest that the prefrontal cortex (PFC) has a role in discrimination of object familiarity in rodents (Akirav and Maroun, 2006) and in recognition memory deficits in patients with MDD (Walter et al., 2007). More particularly, the dopaminergic system in the PFC has been shown to have an important role in memory function in rodents, monkeys and humans (Brozoski et al., 1979; Bubser and Schmidt, 1990; Mizoguchi et al., 2009; Takahashi et al., 2008), supporting a role for agomelatine in recognition memory through an increase in dopaminergic activity in the PFC.

A comparable improvement of object recognition memory was observed with evening and morning administration of melatonin, to the exception of the dose of 40 mg/kg (evening administration). Previously, in the rat elevated plus-maze, an increase in exploratory behaviour was observed following melatonin administration (1 mg/kg) performed in the evening and during the dark phase of the cycle (Golombek et al., 1993). Furthermore, it has been shown in mice that melatonin (20 mg/kg) is able to reverse a scopolamine-induced memory deficit in the passive avoidance task (Agrawal et al., 2008). In the present study, following evening administration, agomelatine at 40 mg/kg increased object recognition memory whereas melatonin at the same dose had no effects. SB 242,084 being active at this dose, these results suggest that effects of agomelatine could be due to its 5-$HT_{2C}$ antagonist properties. Indeed, concerning the antidepressant activity (Bertaina-Anglade et al., 2006a; Papp et al., 2003) and the neuroplastic effects (Molteni et al., 2010; Soumier et al., 2009) of agomelatine, there is some evidence suggesting that these effects may result from the combination of the melatonergic agonist and its 5-$HT_{2C}$ antagonist properties. The combination of both properties may also be important for the effects of agomelatine on object recognition memory.

In order to evaluate the influence of the chronobiotic activity of agomelatine on its facilitating effect in object recognition memory, the administration and the memory task were performed either in the evening or in the morning. Agomelatine and melatonin were shown to be as effective in both conditions. Previously, in a T-maze left–right spatial discrimination procedure, an acute administration of agomelatine (up to 10 mg/kg) has been shown to have a better facilitatory effect on memory performance in the evening than in the morning (Jaffard et al., 1993). These results suggest that a chronobiotic effect may be implicated in some learning processes but not for the object recognition memory.

Because depressive disorders are often associated with cognitive impairment, the assessment of antidepressant treatments on the cognitive function of depressed patients is important. Antidepressant

treatments e.g. selective serotonin reuptake inhibitors (SSRIs) have been evaluated in different animal memory paradigms. A memory impairment was reported following a single administration of fluoxetine (10 mg/kg) in the mouse radial maze (Jaffard et al., 1991) and following a chronic treatment (5 mg/kg) in the rat NOR paradigm (Valluzzi and Chan, 2007). Following chronic treatment, paroxetine (10 mg/kg) did not alter spatial working memory performance of rats in a radial maze, improved temporal order memory performance in a paradigm adapted from the rat NOR task (Naudon et al., 2007) and partially reversed the object recognition memory impairment induced in the chronic mild stress model of depression in mice (Elizalde et al., 2008). In depressed patients, SSRIs such as fluoxetine and escitalopram, and serotonergic–noradrenergic reuptake inhibitors (SNRIs) such as duloxetine improved memory performance assessed by a neuropsychological battery (Gallassi et al., 2006; Herrera-Guzman et al., 2009).

In humans, no deleterious effects of agomelatine on memory function have been reported. Further, in line with previous preclinical results on another memory paradigm (Jaffard et al., 1993), the present data suggest that agomelatine can facilitate episodic memory in rats in a cognitive paradigm requiring little training and inducing a moderate level of stress. Recently, we assessed the effects of agomelatine on learning and memory of rats submitted to a stressful situation by using the fear conditioning paradigm. Following acute administration, agomelatine did not affect the expression of fear memory but disrupted the formation of long-term memory in this fear arousing situation, suggesting that agomelatine may reduce fear memory by counteracting specifically memory consolidation (Diaz-Mataix et al., 2010). Accordingly, in the water-maze procedure, a spatial memory paradigm, chronic agomelatine treatment reversed memory impairment induced by predator exposure, and in parallel, increased hippocampal levels of NCAM in predator-stressed and non-stressed rats, NCAM known to be implicated in memory consolidation (Conboy et al., 2009).

Additionally, chronic agomelatine treatment was shown to modulate the excitotoxic neuromediator glutamate, a key component of molecular plasticity, known to be implicated in memory formation (Robbins and Murphy, 2006; Rodrigues et al., 2004). It has been shown that chronic agomelatine treatment inhibits the increase in depolarisation-evoked release of glutamate induced by an acute stress in rat prefrontal/frontal cortex synaptosomes (Musazzi et al., 2010). Furthermore, chronic agomelatine treatment modulates the neurotrophin brain derived neurotrophic factor (BDNF) that may play an important role in plasticity of the fear-learning circuitry (Choi et al., 2010; Cunha et al., 2010). In fact, chronic agomelatine treatment reverses the down-regulation of BDNF mRNA expression in the hippocampus of glucocorticoid receptor-impaired (GR-i) mice, a transgenic model of depression (Païzanis et al., 2010). Interestingly, Hill et al. (2010) reported a marked increase in levels of the mature form of BDNF in the hippocampus in the 5-$HT_{2C}$ receptor knock-out mice, showing a role of the 5-$HT_{2C}$ receptors in the modulation of the neurotrophin levels. Nevertheless, both the melatonergic and serotoninergic 5-$HT_{2C}$ receptors may be implicated in memory formation as it was shown that an acute agomelatine treatment induces an up-regulation of the BDNF mRNA in the prefrontal cortex and that this increase may result from a functional interaction between both agomelatine's properties (Molteni et al., 2010).

In conclusion, facilitating effects of agomelatine observed on the rat object recognition memory may be beneficial for cognitive deficits described in patients with MDD. These memory facilitating effects of agomelatine could act as a supplementary benefit to its antidepressant effects. The positive effects on memory performance also seen with melatonin and SB 242,084 suggest that agomelatine's effects in the NOR test could depend on both its melatonergic agonistic activity and its antagonistic activity at 5-$HT_{2C}$ receptors as observed for its full antidepressant activity.

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