Pharmacology, Biochemistry and Behavior 100 (2011) 284–288

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Chronic agomelatine and fluoxetine induce antidepressant-like effects in H/Rouen mice, a genetic mouse model of depression

Malika El Yacoubi [a,b,*], Martine Dubois [e,f], Cecilia Gabriel [c], Elisabeth Mocaër [c], Jean-Marie Vaugeois [a,b,d]

[a] Physiopathology of the Neuronal Network Responsible for the Sleep-Waking Cycle Team, CNRS UMR 5292; INSERM U 1028; Lyon Neuroscience Research Center, Lyon, F-69372, France
[b] Université Lyon 1, Faculté de Pharmacie, 69373 Lyon Cedex 08, France
[c] Institut de Recherches Internationales Servier (I.R.I.S), 6 place des Pléiades, 92415 Courbevoie Cedex, France
[d] Université de Rouen, Département de Pharmacologie, U.F.R. Médecine & Pharmacie, 22 Bd Gambetta, 76183 Rouen Cedex 1, France
[e] INSERM U982, DC2N, 76821 Mont Saint Aignan Cedex, France
[f] Université de Rouen, Faculté des Sciences, 76821 Mont Saint Aignan Cedex, France

ARTICLE INFO

Article history:
Received 2 March 2011
Received in revised form 6 July 2011
Accepted 2 August 2011
Available online 5 August 2011

Keywords:
Agomelatine
H/Rouen mice
Fluoxetine
Tail suspension test
Motor activity
Anhedonia

ABSTRACT

The novel antidepressant agomelatine behaves as an agonist at melatonergic MT_1 and MT_2 receptors and as an antagonist at serotonin 5-HT_{2C} receptors. This study investigated the effects of agomelatine and fluoxetine in a genetic model of depression called H/Rouen mice Male and female H/Rouen (helpless line) and NH/Rouen (nonhelpless line) mice, received once daily for 3 weeks agomelatine (10 and 50 mg/kg i.p.), fluoxetine (10 mg/kg i.p.) or vehicle. Immobility duration in the tail suspension test (TST) was assessed on day 1 (D1), day 8 (D8), day 15 (D15) and day 22 (D22). Locomotor activity in a novel environment was assessed on day 18 (D18) and anhedonia (2-bottle sucrose preference test) was considered after the end of chronic treatment, from days 22 to 25. Agomelatine (50 mg/kg) significantly reduced immobility at D15 ($p<0.01$), and D22 ($p<0.001$) in treated H/Rouen mice whereas agomelatine at 10 mg/kg did not induce a statistically significant change. Fluoxetine reduced immobility at D8 ($p<0.01$), D15 ($p<0.001$) and D22 ($p<0.001$). Locomotor activity was unchanged in all treated groups as compared to vehicle groups. In the sucrose test, there was a significant decrease in sucrose preference in H/Rouen mice compared with NH/Rouen mice receiving vehicle. Both agomelatine doses (10 mg/kg ($p=0.05$) and 50 mg/kg ($p<0.001$) as well as fluoxetine ($p<0.001$) significantly increased the sucrose preference in H/Rouen mice as compared with H/Rouen mice that had received vehicle. These data indicate that the novel antidepressant agomelatine has antidepressant-like properties in H/Rouen mice, a genetic model of depression.

1. Introduction

Major depressive disorder is extremely common. It is a leading cause of disability worldwide and has a marked impact on morbidity, mortality and health care costs. In a recent epidemiological study in Western Europe, almost 13% of the population reported a lifetime history of major depressive disorder, and approximately 4% had experienced major depression in the previous 12 months (Alonso et al., 2004). Most current antidepressants interact, more or less selectively, with the monoaminergic systems, in particular the noradrenergic and the serotoninergic systems. This interaction usually takes the form of inhibition of metabolizing enzymes (e.g., monoamine oxidase inhibitors) or inhibition of reuptake systems. Despite these different mechanisms of action, all antidepressants share a slow onset of activity in humans, resulting in a delay of several weeks before maximal antidepressant efficacy is attained. This occurs despite the fact that their interaction with their targets takes place immediately after the first administration. In addition to this slow onset of activity, an additional problem is that not all patients (only around 60–70%) respond to antidepressants. These two drawbacks of antidepressant therapy act synergistically, increasing the period during which symptoms persist (Belmaker and Agam, 2008; Fava and Kendler, 2000). The major challenges for the development of novel antidepressant agents are thus to reduce the delay to maximal effect and to increase the proportion of responders. Several agents have been combined with antidepressant treatment in an attempt to increase the rate of response, increase efficacy or increase the number of responders in line with the idea of multi-target strategies for improving the treatment of depression (Millan, 2006).

Agomelatine is a new antidepressant (de Bodinat et al., 2010) which acts as a potent agonist at the melatonergic receptors MT_1 and MT_2 (Audinot et al., 2003; Yous et al., 1992) and as an antagonist at the 5-HT_{2C} receptor (Millan et al., 2003). These properties have attracted considerable attention, as depressive disorders are worsened by a disturbance of daily rhythms and sleep patterns (Benca and Peterson, 2008; Germain et al., 2008; Kasper et al., 2007; Wirz-Justice

* Corresponding author at: Université Lyon 1, Faculté de Pharmacie, 69373 Lyon Cedex 08, France.
E-mail address: malika.elyacoubi@recherche.univ-lyon1.fr (M. El Yacoubi).

0091-3057/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2011.08.001

and Campbell, 1982). Agomelatine modulates circadian rhythms in rodents (Redman and Francis, 1998; Tuma et al., 2001). Preclinical studies have shown antidepressant-like effects of agomelatine in several animal models, such as the learned helplessness test (Bertaina-Anglade et al., 2006), the chronic mild stress (Papp et al., 2003), the forced swimming test (Bourin et al., 2004) and in a transgenic mouse model of depression (Barden et al., 2005; Paizanis et al., 2009). Antidepressant activity has also been shown in patients with major depressive disorder (Goodwin, 2009; Goodwin et al., 2009; Kennedy, 2009; Kennedy and Emsley, 2006; Loo et al., 2002; Olie and Kasper, 2007).

Depression is a multifactorial illness and genetic factors play a role in its etiology. The understanding of its physiopathology relies on the availability of experimental models potentially mimicking the disease. We have previously reported on a new model developed by selective breeding of Swiss albino outbred CD1 mice with strikingly different responses in the tail suspension test (TST), a stress paradigm aimed at screening potential antidepressants. This selection in the TST has been done with the aim of obtaining two lines of mice called 'helpless' (H/Rouen) and 'non helpless' (NH/Rouen) diverging by their high (> 115 s) and low (< 35 s) immobility scores, respectively. Each mouse of any generation that entered the study was tested three times in the TST at weekly intervals. The helpless line (H/Rouen), which is much more immobile in the TST than the so-called non helpless (NH/Rouen) line, may correspond to a genetic model of depression (El Yacoubi et al., 2003). Thus this genetic model of depression shows great stability in terms of immobility scores and has several features associated with major depressive disorder, such as anhedonia and altered serotoninergic transmission. In the present study, H/Rouen and NH/Rouen mice (from generations S20–S25) were used to compare the effects of agomelatine and fluoxetine in this model of depression.

2. Materials and methods

2.1. Animals

Mice selectively bred in the laboratory facilities for high or low spontaneous "helplessness" in the TST were derived from an original stock of Swiss albino CD1 (Charles River, France) mice (El Yacoubi et al., 2003). The chosen selection criteria, which were the same for each generation, were a high immobility score (> 115 s) for 'helpless' (H/Rouen) and a low immobility score (< 35 s) for 'non-helpless' (NH/Rouen) in the TST. Each mouse of any generation that entered the study was tested 3 times at weekly intervals. They were kept on a 7 a.m.–7 p.m. light cycle with food and water *ad libitum*. Pups were weaned at 21 ± 2 days, and animals were subjected to the first TST at age 35–50 days (middle adolescence). Unless otherwise stated, all experiments were performed with mice from generations S20 to S25 aged 9–18 weeks. For breeding, male and female mice were housed together in pairs. When not under experimentation, they were kept in same-sex groups. Testing was performed between 9 a.m. and 5 p.m. and was in accordance with the European Community Council Directive of 24 November 1986 (86/609/EEC).

2.2. Behavioral studies

2.2.1. Tail Suspension Test (TST)

The TST was performed with a computerized device (ITEM-LABO, France) which allows 6 animals to be tested at one time (Steru et al., 1987). Mice were suspended by the tail with adhesive tape to a hook connected to a strain gauge. The latter transmitted movements to a computer which calculated the total duration of immobility during a 6-min test. Mice that climbed up their tail during the test session were withdrawn from the study. The test was done on D1 (30 min after injection), D8, D15 and D22 in the afternoon at around 14 h, 21 h after the last drug injection.

2.2.2. Locomotor activity

A Digiscan actometer (Omnitech Electronics Inc., Columbus, OH, USA) monitored the horizontal (locomotion) and vertical (rearing) movements of mice. The individual compartments (L = 20; W = 20; H = 30 cm) were put in a dimly lit and quiet room. The horizontal and vertical components of locomotor activity were expressed as number of beams crossed during a 15-min period. This test was done on D18 between 9 h and 14 h corresponding to 16 h to 21 h after the previous drug administration.

2.2.3. Anhedonia (sucrose preference test)

The sucrose test was performed at the end of the experiment because mice were kept in individual cages for this experiment. In the drinking test, mice were given access during 3 days (from D22 to D25) to two bottles, one containing water and the other containing a 2% sucrose solution. Bottles were weighed everyday and their position in the cage was switched daily to prevent possible effects of side-preference in drinking behavior. The preference for sucrose was calculated as a percentage of the consumed sucrose solution relative to the total amount of liquid drunk.

2.3. Drugs

Animals were treated during 3 weeks via the intraperitoneal (i.p.) route with vehicle (HEC 1%), agomelatine 10 or 50 mg/kg (obtained from Servier, France) or fluoxetine 10 mg/kg (kindly donated by Servier, France). For agomelatine, doses were chosen based on its activity over this range of doses in previously tested models of depression such as the forced swim test (Bourin et al., 2004), the chronic mild stress (Papp et al., 2003) or the GR-i mice model of depression (Barden et al., 2005; Païzanis et al., 2010; Barden et al., 2005). For fluoxetine, 10 mg/kg was the dose shown to be active in a previous paper (El Yacoubi et al., 2003).

Treatments were carried out between 4 pm and 5 pm (2–3 h before the dark phase, at 7 pm).

2.4. Statistics

Results are expressed as means ± S.E.M. ANOVAs with or without repeated measures were followed by multiple range test comparisons with the Student–Newman–Keuls *t* test for the difference between means. Significance levels were set at $p<0.05$.

3. Results

3.1. Effects of agomelatine and of fluoxetine in the TST in H/Rouen and NH/Rouen mice

The effects of chronic (3 weeks) administration of vehicle, agomelatine or fluoxetine on the duration of immobility of H/Rouen and NH/Rouen mice in the TST are shown in Fig. 1. No interaction between time and treatment was found with two way ANOVAs with repeated measures ($F_{2,660}=1.03$, $p>0.05$), no effects ($F_{2,660}=0.8$, $p>0.05$) of fluoxetine or agomelatine were observed in NH/Rouen mice as compared with administration of vehicle after 22 days of treatment and no effect of time ($F_{4,660}=2.1$, $p>0.05$) was found.

A two way ANOVA with repeated measures was performed and an interaction between treatment effect and time effect in H/Rouen [$F(12,328=2.48$; $p<0.01$) was found. The separate one way ANOVAs revealed a significant effect of fluoxetine from Day 8 as compared to the vehicle group ($p<0.01$). At Day 15 the effect of fluoxetine ($p<0.001$) and agomelatine 50 mg/kg ($p<0.01$) differed significantly from the vehicle group. At Day 22 both fluoxetine ($p<0.001$) and agomelatine 50 mg/kg ($p<0.001$) significantly decreased the duration of immobility compared to the vehicle group. At 10 mg/kg

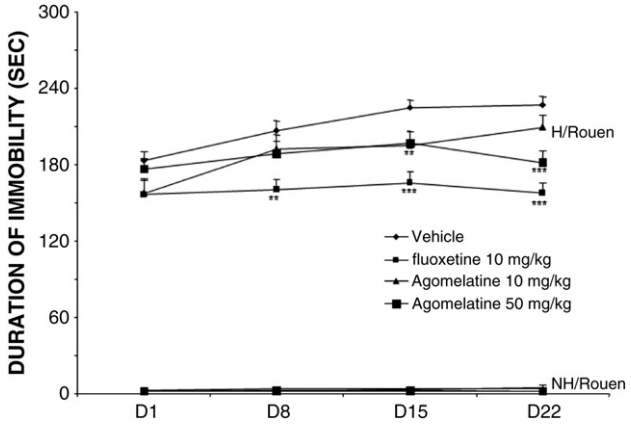

Fig. 1. Evolution of immobility duration in TST of H/Rouen and NH/Rouen lines receiving chronic vehicle or treatments with fluoxetine or agomelatine. Different groups of mice received daily injections of agomelatine 50 mg/kg (H/Rouen: males: $n=20$, females: $n=20$; NH/Rouen: males: $n=20$, females: $n=19$), of agomelatine 10 mg/kg (H/Rouen: males: $n=17$, females: $n=16$; NH/Rouen: males: $n=16$, females: $n=16$), of fluoxetine 10 mg/kg (H/Rouen: males: $n=20$, females: $n=21$; NH/Rouen: males: $n=21$, females: $n=22$), or vehicle (H/Rouen: males : $n=29$, females: $n=26$; NH/Rouen: males: $n=26$, females: $n=28$). D1 (acute), D8 (1 week), D15 (2 weeks), D22 (3 weeks). Graphs depict means ± s.e.m. $^{**}p<0.01$, $^{***}p<0.001$ vs H/Rouen vehicle-treated mice.

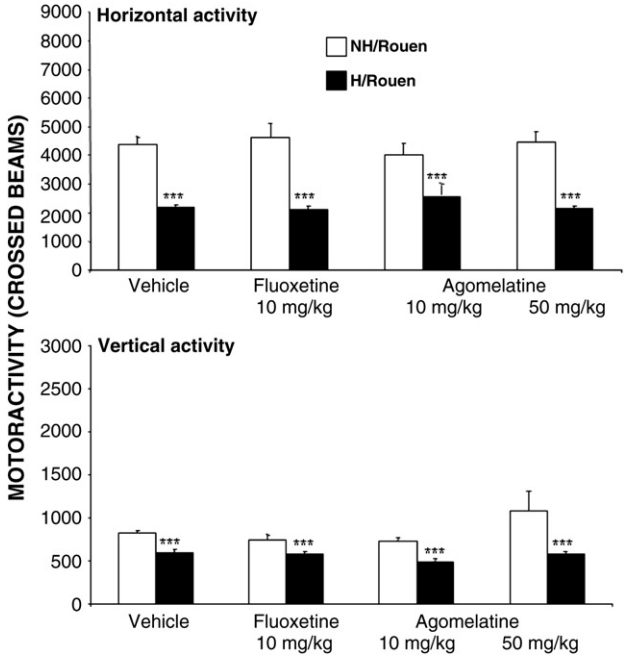

Fig. 2. Locomotor activity in H/Rouen and NH/Rouen mice at day 18. Different groups of mice received daily administrations of agomelatine 50 mg/kg (H/Rouen males $n=16$, H/Rouen females $n=18$; NH/Rouen males $n=19$, NH/Rouen females $n=18$), agomelatine 10 mg/kg (H/Rouen males $n=10$, H/Rouen females $n=8$; NH/Rouen males $n=10$, NH/Rouen females $n=10$), of fluoxetine 10 mg/kg (H/Rouen males $n=15$, H/Rouen females $n=13$; NH/Rouen males $n=15$, NH/Rouen females $n=17$), or vehicle (H/Rouen males $n=21$, H/Rouen females $n=17$; NH/Rouen males $n=22$, NH/Rouen females $n=22$) were tested in an automated actometer on day 18 of treatment. Graph depicts mean ± s.e.m. of crossed beams according to treatments and phenotypes for each gender. $^{***}p<0.001$ vs NH/Rouen mice.

agomelatine decreased slightly but not significantly the duration of immobility in H/Rouen mice at day 15 ($p=0.08$).

3.2. Effects of agomelatine and of fluoxetine in the locomotor activity test in H/Rouen and NH/Rouen mice

A locomotor activity test was performed at day 18 in order to check that a reduction of immobility time would not be the consequence of an increase in locomotor activity (Fig. 2).

In this experiment, H/Rouen mice display a significantly reduced horizontal activity ($F_{1,244}=80.56$, $p<0.001$) and vertical activity ($F_{1,244}=14.25$, $p<0.001$) compared with NH/Rouen mice. No interaction was present between factors lines (helplessness) and treatments in horizontal activity $F_{3,244}=0.76$, $p>0.05$) and vertical activity ($F_{3,244}=1.12$, $p>0.05$). Changes in motor activity across vehicle and treated groups did not reach significance either for H/Rouen or NH/Rouen mice, showing that treatments did not modify motor activity (Fig. 2).

3.3. Effects of agomelatine and fluoxetine on sucrose preference in H/Rouen and NH/Rouen mice (anhedonia)

A sucrose preference test was performed during 3 consecutive days (D22–23, D23–24 and D24–25). It started 24 h after the end of treatments (Fig. 3). There was a significant ($p<0.01$) decrease in preference for the sweetened solution as compared to water in H/Rouen mice that had received vehicle, compared with NH/Rouen mice that had received vehicle. Fluoxetine (10 mg/kg) increased significantly the sucrose preference of H/Rouen mice as compared with H/Rouen mice that had received vehicle ($p<0.001$). Similarly, agomelatine increased significantly the sucrose preference at 10 mg/kg ($p=0.05$) and at 50 mg/kg in H/Rouen mice ($p<0.001$). No effect of either agomelatine or fluoxetine was observed in NH/Rouen mice (Fig. 3).

4. Discussion

H/Rouen mice are a relevant genetic mouse model of depression (El Yacoubi et al., 2003; El Yacoubi and Vaugeois, 2007; Svenningsson et al., 2006). The present results in TST experiments showed a significant antidepressant-like effect of fluoxetine (at a 10 mg/kg daily dose), a reference antidepressant, in H/Rouen mice compared with NH/Rouen mice, thus confirming previous results (El Yacoubi et al., 2003). Under the same experimental conditions, the novel antidepressant agomelatine, which has MT_1 and MT_2 receptor agonist and 5-HT_{2C} antagonist properties, also displayed antidepressant-like effects at the highest dose (50 mg/kg daily). None of the tested

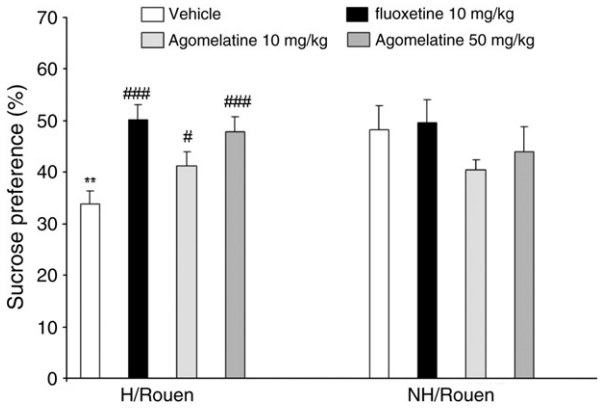

Fig. 3. Sucrose preference at Days 22–25 for mice from vehicle or treated groups. The graph represents the percentages of sucrose solution consumption in relation to whole fluid consumption. Numbers of mice in different groups: H/Rouen male mice: vehicle ($n=15$), fluoxetine 10 mg/kg ($n=11$), agomelatine 10 mg/kg ($n=8$), agomelatine 50 mg/kg ($n=8$), H/Rouen female mice: vehicle ($n=13$), fluoxetine 10 mg/kg ($n=11$), agomelatine 10 mg/kg ($n=8$), agomelatine 50 mg/kg ($n=10$), NH/Rouen male mice: vehicle ($n=11$), fluoxetine 10 mg/kg ($n=10$), agomelatine 10 mg/kg ($n=6$), agomelatine 50 mg/kg ($n=12$), NH/Rouen females: vehicle ($n=15$), fluoxetine 10 mg/kg ($n=11$), agomelatine 10 mg/kg ($n=6$), agomelatine 50 mg/kg ($n=12$). $^{**}p<0.01$ H/Rouen vehicle vs NH/Rouen vehicle. $^{\#}p\leq0.05$, $^{\#\#\#}p<0.001$ drug treated H/Rouen mice vs vehicle treated H/Rouen mice.

drugs modified the behavior of NH/Rouen mice during the TST experiments. In a previous study (Bourin et al., 2004), the acute or repeated (13 days) administration of agomelatine (2, 10 and 50 mg/kg) in Wistar rats, significantly decreased the duration of immobility in the forced swim test (FST), in a manner similar to imipramine. When given for 10 days to Swiss mice, agomelatine, was active in the FST at 4, 16 and 32 mg/kg, whereas the acute administration had no significant effects. This was an effect profile similar to that seen with imipramine. These data and the data reported in the present study suggest that chronic administration of agomelatine is required in order to induce antidepressant-like effects in the FST and TST in mice. This is in agreement with data published by Païzanis et al. (2010), showing that agomelatine (50 mg/kg) reduced immobility in the TST in glucocorticoid receptor-impaired mice (GR-i mice) only after chronic exposure. In the present study agomelatine had no effect at 10 mg/kg in the TST in mice. This differs from what was previously reported at the same dose in rats in the chronic mild stress, learned helplessness test and FST (Papp et al., 2003; Bertaina-Anglade et al., 2006; Bourin et al., 2004), and in mice in the FST (Bourin et al., 2004; Barden et al., 2005). This may be due to species and strain differences, as well as the different models used (Lucki et al., 2001). In the present study fluoxetine reduced the duration of immobility earlier than previously reported in H/Rouen mice (i.e. D8 vs. D22)(El Yacoubi et al., 2003). Interestingly, in recent experiments we saw no significant effect of fluoxetine 10 mg/kg before day 22 in H/Rouen mice (data not shown).

The anti-immobility effects of the two antidepressants in the TST are unlikely to be due to effects on motor activity. In the present study a difference in basal motor activity was found between NH/Rouen and H/Rouen mice (lower levels in the latter line) as previously shown (El Yacoubi et al., 2003). The motor activity experiment showed a lack of stimulant or depressant effect of the tested antidepressants after repeated administration. This suggests that an increase in motor activity does not explain the antidepressant-like effects of the drugs. This is in accord with a previous study, in which the acute or repeated administration of agomelatine in mice did not modify their locomotor activity (Bourin et al., 2004). There are reports in mice showing either a decrease in locomotion after fluoxetine 15 mg/kg i.p. (Brookshire and Jones, 2009) or a slight increase in locomotion after 10 mg/kg s.c. (Brocco et al., 2002).

The sucrose consumption model assesses a different aspect of depressive behavior, anhedonia which is a core symptom of depression, and was originally used to assess the depressive effects of chronic mild stress (Papp et al., 1991). It has since been used in several other models of depression (El Yacoubi et al., 2003; Pucilowski et al., 1993; Shumake et al., 2005; Strekalova et al., 2004). H/Rouen and NH/Rouen mice behaved differently in the sucrose preference test. H/Rouen mice receiving vehicle showed a reduced sucrose intake as compared with NH/Rouen controls. This confirms the differences reported previously (El Yacoubi et al., 2003). When chronically administered to H/Rouen mice, both agomelatine doses (10 and 50 mg/kg), as well as fluoxetine (10 mg/kg) counteracted the anhedonia observed in this model. This confirms the antidepressant effects of agomelatine. This additional evidence of an antidepressant-like effect of agomelatine and fluoxetine based on recovery of preference for a sweetened drink further reinforces the hypothesis that the effects of the drugs on TST are not the result of a confounding effect of general motor activity. In addition, these data are in agreement with data showing the antidepressant effects of agomelatine, at the same doses, in the chronic mild stress model of depression in rats (Papp et al., 2003). Thus, agomelatine, an antidepressant with a novel mechanism of action, has been shown to e to antagonize after a chronic treatment the anhedonic state which characterizes the H/Rouen line. In the l tests that explored an antidepressant-like effect used in the present study, agomelatine was active in the 10–50 mg/kg dose range, suggesting that the range of efficacious doses in mice is similar to that reported in rats (Papp et al., 2003).

In conclusion, the present data show that the novel antidepressant agomelatine has antidepressant-like properties in H/Rouen mice, a genetic model of depression. Its novel mechanism of action deserves further studies. Moreover, these data show that the antidepressant activity of drugs with different mechanisms of action can be demonstrated in this genetic animal model of depression, reinforcing its potential as a screening tool for the discovery of new antidepressant drugs.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.pbb.2011.08.001.

References

Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, et al. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl 2004:21–7.

Audinot V, Mailliet F, Lahaye-Brasseur C, Bonnaud A, Le Gall A, Amosse C, et al. New selective ligands of human cloned melatonin MT1 and MT2 receptors. Naunyn Schmiedebergs Arch Pharmacol 2003;367:553–61.

Barden N, Shink E, Labbe M, Vacher R, Rochford J, Mocaer E. Antidepressant action of agomelatine (S 20098) in a transgenic mouse model. Prog Neuropsychopharmacol Biol Psychiatry 2005;29:908–16.

Belmaker RH, Agam G. Major depressive disorder. N Engl J Med 2008;358:55–68.

Benca RM, Peterson MJ. Insomnia and depression. Sleep Med 2008;9(Suppl. 1):S3–9.

Bertaina-Anglade V, la Rochelle CD, Boyer PA, Mocaer E. Antidepressant-like effects of agomelatine (S 20098) in the learned helplessness model. Behav Pharmacol 2006;17:703–13.

Bourin M, Mocaer E, Porsolt R. Antidepressant-like activity of S 20098 (agomelatine) in the forced swimming test in rodents: involvement of melatonin and serotonin receptors. J Psychiatry Neurosci 2004;29:126–33.

Brocco M, Dekeyne A, Veiga S, Girardon S, Millan MJ. Induction of hyperlocomotion in mice exposed to a novel environment by inhibition of serotonin reuptake. A pharmacological characterization of diverse classes of antidepressant agents. Pharmacol Biochem Behav 2002;71:667–80.

Brookshire BR, Jones SR. Direct and indirect 5-HT receptor agonists produce gender-specific effects on locomotor and vertical activities in C57 BL/6J mice. Pharmacol Biochem Behav 2009;94:194–203.

de Bodinat C, Guardiola-Lemaitre B, Mocaër E, Renard P, Muñoz C, Millan MJ. Agomelatine, the first melatonergic antidepressant: discovery, characterization and development. Nat Rev Drug Discov 2010;9:628–42.

El Yacoubi M, Vaugeois JM. Genetic rodent models of depression. Curr Opin Pharmacol 2007;7:3–7.

El Yacoubi M, Bouali S, Popa D, Naudon L, Leroux-Nicollet I, Hamon M, et al. Behavioral, neurochemical, and electrophysiological characterization of a genetic mouse model of depression. Proc Natl Acad Sci U S A 2003;100:6227–32.

Fava M, Kendler KS. Major depressive disorder. Neuron 2000;28:335–41.

Germain A, Buysse DJ, Nofzinger E. Sleep-specific mechanisms underlying posttraumatic stress disorder: integrative review and neurobiological hypotheses. Sleep Med Rev 2008;12:185–95.

Goodwin GM. Clinical studies on the efficacy of agomelatine on depressive symptoms. CNS Drugs 2009;23(Suppl 2):35–9.

Goodwin GM, Emsley R, Rembry S, Rouillon F. Agomelatine prevents relapse in patients with major depressive disorder without evidence of a discontinuation syndrome: a 24-week randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2009;70:1128–37.

Kasper S, Hajak G, Wulff K, Hoogendijk WJ, Montejo AL, Smeraldi E, et al. Efficacy of the novel antidepressant agomelatine on the circadian rest-activity cycle and depressive and anxiety symptoms in patients with major depressive disorder: a randomized, double-blind comparison with sertraline. J Clin Psychiatry 2007;71:109–20.

Kennedy SH. Agomelatine: efficacy at each phase of antidepressant treatment. CNS Drugs 2009;23(Suppl. 2):41–7.

Kennedy SH, Emsley R. Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. Eur Neuropsychopharmacol 2006;16:93–100.

Loo H, Hale A, D'Haenen H. Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT(2C) antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. Int Clin Psychopharmacol 2002;17:239–47.

Lucki I, Dalvi A, Mayorga AJ. Sensitivity to the effects of pharmacologically selective antidepressants in different strains of mice. Psychopharmacol (Berl) 2001;155:315–22.

Millan MJ. Multi-target strategies for the improved treatment of depressive states: conceptual foundations and neuronal substrates, drug discovery and therapeutic application. Pharmacol Ther 2006;110:135–370.

Millan MJ, Gobert A, Lejeune F, Dekeyne A, Newman-Tancredi A, Pasteau V, et al. The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine2C receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. J Pharmacol Exp Ther 2003;306:954–64.

Olie JP, Kasper S. Efficacy of agomelatine, a MT1/MT2 receptor agonist with 5-HT2C antagonistic properties, in major depressive disorder. Int J Neuropsychopharmacol 2007;10:661–73.

Paizanis E, Renoir T, Lelievre V, Saurini F, Melfort M, Gabriel C, et al. Behavioural and neuroplastic effects of the new-generation antidepressant agomelatine compared to fluoxetine in glucocorticoid receptor-impaired mice. Int J Neuropsychopharmacol 2009:1–16.

Païzanis E, Renoir T, Lelievre V, Saurini F, Melfort M, Gabriel C, Barden N, Mocaër E, Hamon M, Lanfumey L. Behavioural and neuroplastic effects of the new-generation antidepressant agomelatine compared to fluoxetine in glucocorticoid receptor-impaired mice. Int J Neuropsychopharmacol 2010;13:759–74.

Papp M, Willner P, Muscat R. An animal model of anhedonia: attenuation of sucrose consumption and place preference conditioning by chronic unpredictable mild stress. Psychopharmacol (Berl) 1991;104:255–9.

Papp M, Gruca P, Boyer PA, Mocaer E. Effect of agomelatine in the chronic mild stress model of depression in the rat. Neuropsychopharmacology 2003;28:694–703.

Pucilowski O, Overstreet DH, Rezvani AH, Janowsky DS. Chronic mild stress-induced anhedonia: greater effect in a genetic rat model of depression. Physiol Behav 1993;54:1215–20.

Redman JR, Francis AJ. Entrainment of rat circadian rhythms by the melatonin agonist S-20098 requires intact suprachiasmatic nuclei but not the pineal. J Biol Rhythms 1998;13:39–51.

Shumake J, Barrett D, Gonzalez-Lima F. Behavioral characteristics of rats predisposed to learned helplessness: reduced reward sensitivity, increased novelty seeking, and persistent fear memories. Behav Brain Res 2005;164:222–30.

Steru L, Chermat R, Thierry B, Mico JA, Lenegre A, Steru M, et al. The automated Tail Suspension Test: a computerized device which differentiates psychotropic drugs. Prog Neuropsychopharmacol Biol Psychiatry 1987;11:659–71.

Strekalova T, Spanagel R, Bartsch D, Henn FA, Gass P. Stress-induced anhedonia in mice is associated with deficits in forced swimming and exploration. Neuropsychopharmacology 2004;29:2007–17.

Svenningsson P, Chergui K, Rachleff I, Flajolet M, Zhang X, El Yacoubi M, et al. Alterations in 5-HT1B receptor function by p11 in depression-like states. Science 2006;311:77–80.

Tuma J, Strubbe JH, Mocaer E, Koolhaas JM. S20098 affects the free-running rhythms of body temperature and activity and decreases light-induced phase delays of circadian rhythms of the rat. Chronobiol Int 2001;18:781–99.

Wirz-Justice A, Campbell IC. Antidepressant drugs can slow or dissociate circadian rhythms. Experientia 1982;38:1301–9.

Yous S, Andrieux J, Howell HE, Morgan PJ, Renard P, Pfeiffer B, et al. Novel naphthalenic ligands with high affinity for the melatonin receptor. J Med Chem 1992;35:1484–6.