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Study of Antidepressant and Anxiolytic Effects of Agomelatine and Fluoxetine in Mice

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Abstract

Objectives: Chronic restraint stress (CRS) has been used to model depression-like behaviors in rodents. We know that serotonin receptor (5-HT2C) is a common antidepressant mechanism and we also know the difference in antidepressant mechaism of agomelatine and fluoxetine. However, we do not know the exact difference between the antidepressant-like and anti-anxiety effects of agomelatine and fluoxetine in the CRS-induced depression-like behavior in mice. In this study, the similarities and differences of the antidepressant effects of agomelatine and fluoxetine on anxiety- and depression-like behaviors were evaluated in a mouse model of chronic restraint stress (CRS) through behavior test.

Materials and methods: CRS procedure (6 hours/day, 4 weeks) was performed as a typical stress model to study anxiety and depression along with agomelatine(60mg/kg) or fluoxetine(15mg/kg) treatment (intragastric, once/day, 4 weeks), which began simultaneously with CRS. Behavioral experiments including open field, elevated plus maze, forced swimming test and sucrose preference test were assessed to evaluate the anti-anxiety and anti-depressive effects.

Results: CRS induced depressive-like behaviors and not anxiety-like behaviors. Agomelatine (60mg/kg) or fluoxetine (15mg/kg) treatment prevented CRS-induced increase in the immobility time in the forced swim and the decrease sucrose preference in sucrose preference test. And he immobility time of Age group was significantly longer than Flu group. However, no alterations were observed in the open field test and Elevated plus maze.

Conclusion: CRS induced depressive-like behaviors and not anxiety-like behaviors. Agomelatine and fluoxetine could reverse this depression-like behavior.

Keywords: Depressive Disorder, Chronic Restraint Stress (CRS), Agomelatine, Fluoxetine, Anxiety, Behavior Test

Introduction

Depression is characterized by depressed mood, anhedonia, low self-esteem, loss of motivation, sleep disruption, loss of appetite, and other cognitive symptoms [1]. Symptoms of depression are highly prevalent, affecting up to 27% of the general population according to recent meta analytic data [2]. However, the exact biological, psychological and social mechanisms underlying the pathogenesis of depression remain largely unknown. Due to the intricate mechanism of depression, many clinical antidepressants are inefficient, approximately 33% of patients with depression exhibit little or no improvement when treated with existing conventional antidepressants, which commonly act on the monoaminergic systems and further contributing to the global burden of the disease. Statistical estimation revealed that among 29 common conditions and diseases in terms of incidence, prevalence, and disability-adjusted life years [3]. Depression ranked first in population-wide burden by disability-adjusted life years [4].

Chronic exposure to highly stressful situations is detrimental to the wellbeing of both body and brain. Chronic stress, especially during the unique developmental timeframe of adolescence and early adulthood, can have adverse effects on both behavioral and metabolic outcomes later in life. Chronic exposure to stress dysregulates the hypothalamic-pituitary-adrenal (HPA) axis causing an increase in systemic inflammation resulting in increased risk of psychiatric disorder, such as depression [5-6]. Chronic exposure such as CRS has been widely used to study the hormonal, behavioral alteration and morphological in several brain regions in rodents, such as the hippocampus, prefrontal cortex, amygdala, and nucleus accumbens because it is inexpensive and relatively easy to implement [7]. Depending on duration and intensity of chronic stress, most studies reported that exposure of animals to CRS induces depression-like behaviors such as anhedonia, but the result of anxiety like behaviors are vary.

Agomelatine is a relatively new antidepressant with a mechanism of action that is different from other antidepressants: it is a melatonergic agonist and a 5-HT2C antagonist. It has shown an

antidepressant effect in preclinical models, and the results of a large-scale clinical trial program, conducted in MDD, indicate both an antidepressant activity and a favorable tolerability profile. At the same time, agomelatine emerged as one of three 'preferable' antidepressants based on the dual measures of efficacy and tolerability after 8 weeks of treatment.

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Therefore, it is interesting to re-evaluation the behavioral tests in mouse exposed to chronic restraint stress. Simultaneously, we aimed to investigate the discrepancy in antidepressant-like and anti-anxiety effects of agomelatine and fluoxetine in the model of CRS.

Materials and Method

Animals

Male C57BL/6N mice (weighing 20 ±2g, 8 weeks old) were used in this study. The mice were maintained in a room at 24 ± 1 °C with 50%–60% relative humidity under a 12-h light/dark cycle (lights on at 09:00) with free access to food and water. All experimental procedures were approved and performed according to the Animal Care and Use Committee of the Institute of Zhejiang University, China. Animal Ethics Number is ZJU20160267.

Study design and drug administration

After 2 weeks of adaptation, the mice were randomly assigned to 3 groups of 8 mice each: the chronic restraint stress (CRS) group, CRS+ fluoxetine (Patheon, France) group, the CRS + agomelatine (Lianyungang, China) group.

From Day 1 to Day 28, the 10 mice in the CRS group were subjected to CRS and intragastric administration of 8.0ml/kg saline daily. Mice in the CRS + agomelatine group and the CRS + fluoxetine group were subjected to CRS and intragastric administration of agomelatine (60mg/kg/d, 7mg agomelatine dissolved in 1ml saline) and fluoxetine (15mg/kg/d, 2mg fluoxetine dissolved in 1ml saline) respectively, half an hour before daily stress. The stress of fluoxetine and agomelatine were based on previous study [8].

The Chronic Restraint Stress model

The CRS model was based on the Chiba method [9], with slight modification. Mice in the CRS, CRS+ agomelatine (Ago) and CRS+ fluoxetine (Flu) were exposed to CRS for 28 consecutive days.

Behavioral Testing

All animals were brought to the testing room at least 30 min before the start of each behavioral test and remained in the same room throughout the test. Tests were conducted during the light cycle. Tests were applied in the following sequence : 1) Open Field Test (OFT), 2) elevated plus maze(EPM); 3)forced swim test (FST),4) Sucrose Preference Test (SPT). Most behaviours were performed during the light phase except for the sucrose preference test, which was performed during the dark phase to maximize the consumption of solution, and the open field test for CRS mice.

1. Open Field Test (OFT)

The apparatus consisted of a white Plexiglas box (45cm × 45 cm × 45 cm) divided into two zones: outer square (periphery) and inner square (center). Each mouse was placed in the center of the box and freely explored the environment in a room with dim light for 5 min. The movement of mouse was recorded by the automatic behavior-tracking system (Video Track, Viewpoint Inc., France). The calculated standard measures were: (1) total distance and sm0.all distance traveled (cm); (2) time spent in the central zone (s) vs total time in %.

2. Elevated plus maze (EPM)

Elevated plus maze apparatus consisted of two opposite-facing closed arms (30 cm × 5 cm × 15 cm), two opposite-facing open arms (30 cm × 5 cm) and a central area (5 cm × 5 cm), and the maze was 50 cm above the ground. For the elevated plus maze, the mouse was placed in the center of the maze facing one of the two closed arms for a 5-minute test. Were recorded using an automatic analyzing system (ANY-maze, Stoelting Inc., USA). The number of entries and time spent in the open arms were recorded using an automatic analyzing system (ANY-maze, Stoelting Inc., USA).

3. Forced swim test (FST)

Mice were placed into cylinder (12 cm diameter, 25 cm height) filled with 24 ± 1°C water. Water depth was set to prevent animals from touching the bottom with their tails or hind limbs. Two mice at a time were videotaped from the side. A cardboard divider separated the cylinders so that the mice could not see each other during the trials. The mouse activity was video recorded for 6 min, and the duration of immobility was recorded during the last 4 min of the 6-min test. After test session, mice were placed in a clean cage containing paper towels under a heat lamp until dry. Immobility was defined according to criteria described [10].

4. Sucrose Preference Test (SPT)

The SPT was performed as previously reported with slight modification [11]. Mice were single housed and each mouse was adapted to a 2% sucrose solution (w/v): 24 h exposure to two bottles of sucrose solution and an additional 24 h exposure to one bottle of 2% sucrose solution on the right side of each cage and one bottle of water on the left side. Then, all the mice were then water and food deprived for 24 h and then exposed to one bottle of 2% sucrose and one bottle of water for 2 h in the dark phase. Bottle positions were switched after 1 h (for 2 h test). Total consumption of each fluid was measured and sucrose preference was defined as the average sucrose consumption ratio during the first and second hours. Sucrose consumption ratio was calculated by dividing the total consumption of sucrose by the total consumption of both water and sucrose.

Statistical Analysis

Each value was presented as a mean ± standard (SEM) deviation and analyzed with ANOVA using SPSS 22.0 software. Histograms were generated in GraphPad Prism 8. Gray values of western blot results were calculated by using Image Lab software. Immunofluorescence results of Iba1 were analyzed by using Pro Image Plus. A value of $P < 0.05$ was considered significant.

Results

Effects of Agomelatine/Fluoxetine on body weight of CRS-induced mice

The body weight was monitored every other day during chronic restraint stress and drug treatment. No significant differences were found in the baseline body weight among groups ($F_{2, 21}$= 1.847, P = 0.182; Figure 1). There was no difference among groups Day7, agomelatine and fluoxetine increased the weight of mice ($F_{2, 21}$= 9.823, P <0.01; Figure 1).

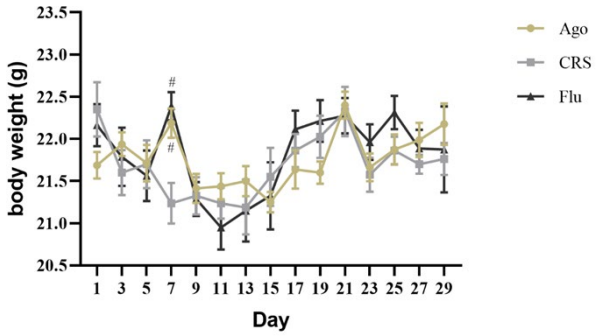

Figure 1: Effects of chronic restraint stress and drug treatment on body weight. The values represent mean ± SEM. N = 8. (#P<0.05, compared with CRS on day 7; One-way repeated measures analysis of variance).

Effects of Agomelatine/Fluoxetine on Open Field test of CRS-induced mice

One way ANOVA showed evidence of the anxiety-like behaviors, However, no significant effect was observed in the number of entries into, the time spent in central zone and the locomotor activity of the OFT (Fig.2 A–C) among groups.

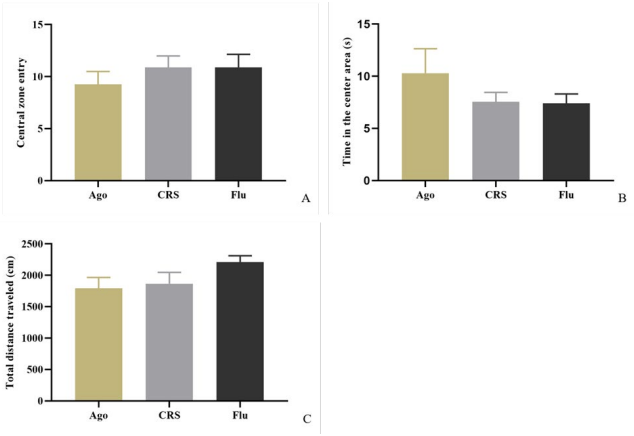

Figure 2: the changes of Open field test in each group. Central zone entry (A), time in the center area (B) and total distance traveled (C) in the open field test. The values represent mean ± SEM. N = 8. (One-way ANOVA).

Effects of Agomelatine/Fluoxetine on elevated plus maze of CRS-induced mice

The CRS protocol did not alter the number of entries into, time spent in the open arms and the locomotor activity in the EPM (Fig.3 A–C)

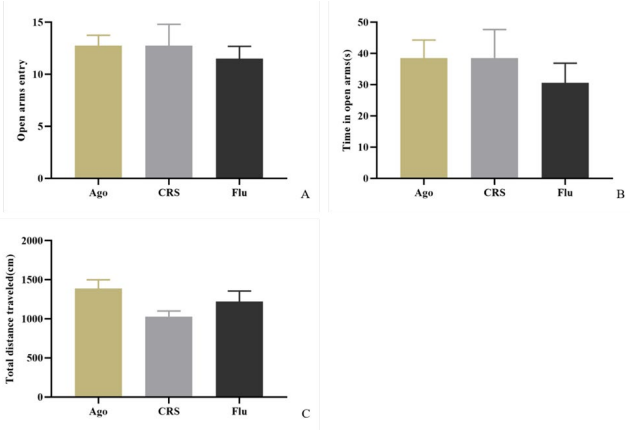

Figure 3: the changes of elevated plus maze in each group. Open arms entry (A), time in open arms (B) and total distance traveled (C) in the elevated plus maze. The values represent mean ± SEM. N = 8. (One-way ANOVA).

Effects of Agomelatine/Fluoxetine on forced swim test of CRS-induced mice

Figure 4 depicts the average activity of different groups recorded in the forced swim test using one-way ANOVA. One-way ANOVA showed that there was a significant difference in time spent in the different parameters between groups [$F_{(2,21)}$ =13.721; p<0.0001].

The post hoc test showed that the immobility time was significantly shorter in Ago and Flu groups compared to the CRS (p< 0.01). The immobility time of Ago group was significantly longer than Flu group (p<0.05).

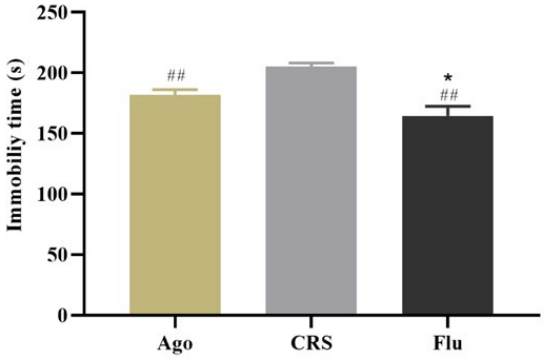

Figure 4: The immobility time in forced swimming test each group. The values represent mean ± SEM. N = 8. (##P<0.01, compared with CRS; *P<0.05, compared with Ago group; one-way ANOVA).

Effects of Agomelatine/Fluoxetine on sucrose preference test of CRS-induced mice

Figure 5 depicts the average liquid intake assessed in the sucrose preference test after chronic Restraint stress and administration of agomelatine/fluoxetine. Post hoc test showed that CRS consumed more water [$F_{(2,21)}$ = 4.97; p< 0.05] than the Ago and Flu groups. The sucrose consumption ratio further showed that CRS consumed significantly less sucrose than the Ago and Flu groups alone [$F_{(2,21)}$ = 7.60; p< 0.01]. But there was no significant difference between Ago and Flu groups. (P>0.05)

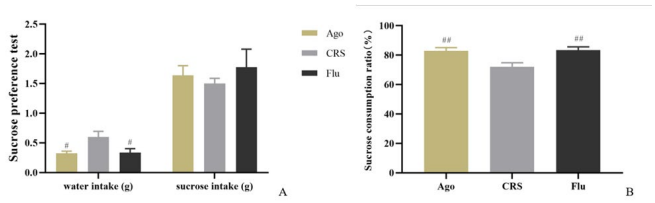

Figure 5: Effects of Agomelatine/Fluoxetine on sucrose preference test. Water and sucrose consumed(A), sucrose consumption ratio(B). The values represent mean ± SEM. N = 8. (#P<0.05, compared with CRS; ##P<0.01, compared with CRS; one-way ANOVA).

Discussion

Chronic restraint stress is a non-invasive protocol, which is very similar to human psychological stress and making it a reliable animal model of depression with good replicability [12]. In our study, the body weight and a battery of well-established behavioral tests aiming at measuring locomotor behavior, anxiety-related behaviors and depression-related behaviors was used to assess CRS-induced behavioral alterations. However, unlike many studies that report a reduction of body weight gain during or after chronic stress we did not find a significant reduction of body weight gain during the chronic stress period, similar to the results of Macedo et al. [13,14]. After CRS protocol, we observed that decreased sucrose preference and increased immobility in the FST and agomelatine could alleviate the depressive behaviors respectively. However, no significant effect of CRS was observed in the EPM or OFT, suggesting no cooccurrence of anxiety-like behavior which is consistent with recent studies have reported [15]. However, other studies have not confirmed such behavioral changes after CRS [16-18]. Reasons for this discrepancy might be attributed to the properties of the restraint stress (e.g., frequency and duration) [19]. Other experimental conditions, such as the strain of rodent used, living habitation, circadian rhythm, and a reversed light/dark cycle, might also affect behavioral outcomes after CRS.

The forced swim test showed a decrease in immobility time in Ago group and Flu group compared to the CRS group, showing a pronounced depressive behavior in the CRS group. However, the immobility time in FST showed that fluoxetine is more effective in improving behavioral despair compared to agomelatine. Behavioral despair in animals assessed in forced swim test have been related to an increase in immobility time. Besides an increase in immobility time as a core of behavioral despair, anhedonia has been also shown as a core of depression. The mouse in CRS group consumed less sucrose compared to the Ago and Flu groups, but the differences between Ago and Flu group were not discovered.

The elevated plus maze is a widely used behavioral assay for rodents and it has been validated to assess the anti-anxiety effects of pharmacological agents and steroid hormones, and to define brain regions and mechanisms underlying anxiety-related behavior. The number of entries into the open arms and the time spent in the open arms are used as indices of open space-induced anxiety in mice. Unlike other behavioral assays used to assess anxiety responses that rely upon the presentation of noxious stimuli (e.g., electric shock, food/water deprivation, loud noises, etc.) that typically produce a conditioned response, the elevated plus maze relies upon rodents' proclivity toward dark, enclosed spaces (approach) and an unconditioned fear of heights/open spaces (avoidance). Variable subjects related to animal such as strain, sex/gender, estrous cycle and age that need to be considered when setting up an experiment using the elevated plus maze [20-25]. And as well as the external housing conditions. After excluding these conditions, we did not find any differences among groups either, which in agreement with recent studies have reported [13].

The OFT was designed to assess the locomotor activity of rodents. Animals displayed decreased locomotor activity in OFT after CRS, which indicates the loss of exploration and interest, two instinctive activities of normal animals in a novel environment [18,26]. Since there was no significant statistical difference between the agomelatine or fluoxetine and CRS groups in the OFT, suggesting CRS procedure failed to induce cooccurrence of anxiety-like behavior in this study.

Agomelatine represents a different approach to the treatment of major depressive disorder divorced from the traditional approaches of direct effects on monoamine reuptake mechanisms. The combination of serotonergic antagonism and melatonin agonism is unique in depression treatments. Both actions combined are necessary for antidepressant efficacy [27]. However, the mechanism is also manifested in fluoxetine, that is, serotonin receptor (5-HT2C) antagonism, which is also the common of the two drugs. Treatment with agomelatine/fluoxetine both reversed the depression-like behaviors in animals subjected to chronic restraint stress, resulting in a reduction of freezing time in FST and a better sucrose preference. These results suggest that both melatonin agonist and selective serotonin antagonist exert the effect of antidepressant. The biological mechanism of depression may involve 5-HT2C or melatonin receptors, but this is one of the mechanisms in depression, and improving one of them can improve depression. In addition, it could be possible that increased serum BDNF level, fall in serum TNF-α level and HPA axis alterations caused by agomelatine and fluoxetine may have contributed to their antidepressant response [28-29].

Although most Antidepressants (ADs) produce similar behavioral and neuroplastic effects, each AD has a characteristic pharmacological and molecular signature, the full exploitation of which could be helpful in designing treatments that capture the various pathological facets presented by individual depressed patients. To this end, we will further to identify to identify common and divergent molecular targets and pathways of two distinct classes of ADs, represented by fluoxetine and agomelatine. Despite their diverse pharmacological profiles, all of the two drugs result in similar behavioral outcomes, suggesting overlapping mechanisms of action. Insights into their potentially common molecular targets and divergent mechanisms may help develop new treatment strategies that exploit specific properties of each individual drug.

Conclusion

CRS induced depressive-like behaviors and not anxiety-like behaviors. Agomelatine and fluoxetine could reverse this depression-like behavior. Fluoxetine had a better effect on improving behavioral despair than agomelatine.

Acknowledgment

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