Original Article

BENEFICIAL INFLUENCE OF AGOMELATINE TREATMENT ON BEHAVIORAL IMPAIRMENTS IN AB-INDUCED RAT MODEL OF ALZHEIMER'S DISEASE

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Summary

An increased risk of developing Alzheimer's disease (AD) exists in patients with a history of depression. In the present study, we demonstrated that chronic agomelatine intraperitoneal treatment, at a dose of 40 mg/kg for 21 days, starting one month after inducing AD by intracerebroventricular injection of amyloid-beta (Aβ) corrected anhedonia, decreased anxiety, and showed a potential to mitigate working memory errors during the last session in a radial arm maze. Altogether, our findings suggest that chronic agomelatine administration treatment could alleviate the burden of AD and may be considered a promising therapeutic approach to some adverse symptoms caused by the disease.

Keywords: Alzheimer's disease, amyloid-beta, agomelatine, depression

Introduction

Depression is linked to dementia during the last decades, based on strong neurobiological and epidemiological evidence. Depression and dementia were traditionally considered as two completely different disorders. However, pathophysiological mechanisms in AD and depression have been recently discovered to function in very similar ways. These findings can help understand why a history of depression is currently considered as a factor that significantly increases the risk of AD and other types of dementia [1]. Melatonin has been shown to have a beneficial role in models of AD [2]. Experimental findings suggest that, compared to selective serotonin reuptake inhibitors (SSRIs), the antidepressant agomelatine has advantages as a circadian phase-shifting agent.

Epidemiological and neurobiological evidence suggests a strong relationship between depression and dementia. For a while, depression and dementia were regarded as entirely distinct clinical entities. Recent findings suggest that depression may be considered a risk factor for dementia and Alzheimer's disease (AD) in particular. Common pathophysiological mechanisms between these two conditions have been identified, which might explain the progression from depression

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to AD [1]. Experimental findings suggest that the melatonin system has a beneficial role in models of AD [2]. The antidepressant agomelatine has been found to have advantages over SSRIs as a circadian phase-shifting agent [3]. Its action mechanism involves a combined agonism on MT1/MT2 melatonin receptors and antagonism on 5-HT2C on serotonin receptors. Our previous studies suggest that this melatonin analogue has a potential role in protecting the central nervous system and alleviating anhedonia when applied to the streptozotocin-induced rat model of AD [4][5].

In the present study, we aimed to confirm and expand our findings in another rat model of AD induced by amyloid-beta (Aβ).

Materials and Methods

The procedures used in this study were conducted according to the European Communities Council Directive 2010/63/EU for animal experiments. The experiments were conducted per national rules on animal experiments and were approved by the Bulgarian Food Safety Agency.

Animals

Eight-week-old male Wistar, Male Sprague Dawley rats, weighing 200–230 g were obtained from the animal breeding facility of the Institute of Neurobiology, Bulgarian Academy of Sciences. They were housed in groups of n=3–4 animals per cage and kept under standard conditions (12 h light/12 h dark, at a temperature of 22-23°C, 50–60% relative humidity) with food and water ad libitum.

Three experimental groups of animals were studied: sham-veh (intracerebroventricular (icv) injection of a vehicle only), Aβ-veh (treated with Amyloid β only), and Aβ-Ago (AD model rats, treated with agomelatine).

Surgery

The implantation of the cannulas was performed according to protocols used in a previous study ([5)]. Rats anesthetized with ketamine (80 mg/kg, i.p.) and xylazine (20 mg/kg, s.c.) were fixed on a stereotaxic apparatus to insert cannulas bilaterally in the lateral ventricles (AP = - 0.8, L = ± 1.5, H = 3.8) [5]. The Aβ (1μg/5 μl), dissolved in 6 μl artificial cerebrospinal fluid (ACSF), was incubated for 24h at room temperature before the intracerebroventricular injection over 5 min using a 10-μl Hamilton® syringe. The same procedure was applied to the sham-veh group, except that only CSF was administered. Thirty days after the surgery, rats were treated i.p. with Ago (40 mg/kg) for the following 30 days.

Behavioral tests

The interactions between anxiety and depression-related behaviors, as studied in various tasks in rat animal models, are described after Balmus et al. [6] (Figure 1). Behavioral tests for testing the anxiety, depressive-like behavior, and spatial memory were performed during the last ten days of treatment with agomelatine.

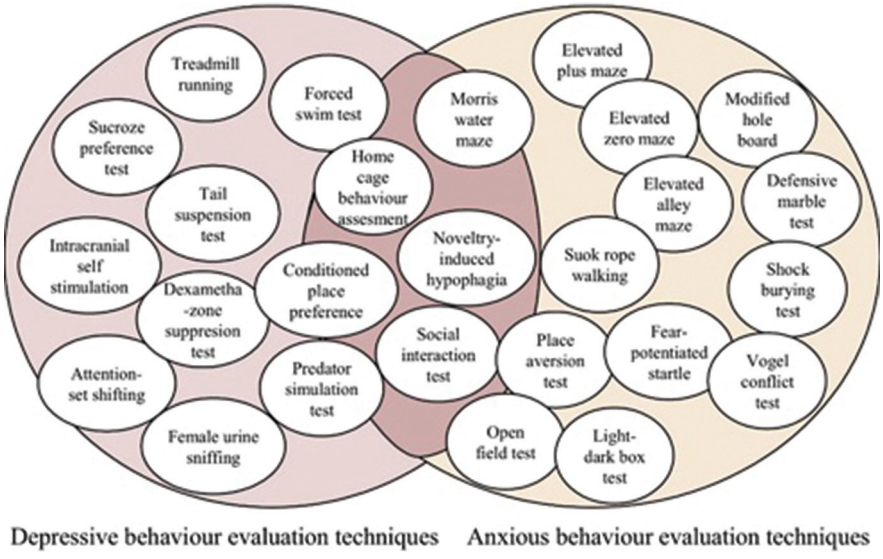

Figure 1. Behavioral tests

Elevated Plus Maze (EPM)

EPM is considered an important test that evaluates anxiety-like behavior by counting the number of entries and time spent in the open arms [7]. This test is based on the natural aversion of rodents for open spaces. Each animal was used just once. All sessions were recorded using a camera and video-tracking system (SMART PanLab software, Harvard Apparatus, USA) that provided recordings of all sessions. The number of entries and time spent in the open arms was recorded. When all four rat limbs were within an arm, this was counted as an arm entry [8]. The apparatus was cleaned with ethanol solution and dried with a cloth before the next animal was tested.

Open Field (OF) test

The rationale behind the open field test is the same as that behind the EPM test. In contrast to the EPM, higher degrees of freedom is offered to the test animals. Thus, more complex behaviors can be displayed in the open field, making interpretation of the results more complicated. Rodents typically spend a more significant amount of time exploring the periphery of the arena, usually in contact with the walls (thigmotaxis), avoiding the unprotected center area [9]. We calculated the time in the center and total distance in the OF.

Forced Swimming Test (FST)

The FST is another reliable screening tool for depressive-like behavior, described as the gold standard for assessing the activity of antidepressants [10]. The procedure consists of a pre-test and an actual test session (each lasting 5 mins). Both sessions were executed in a narrow cylinder filled with water. The time spent struggling not to drown, and swimming was compared to that spent in immobility and passive floating [10].

Radial Arm Maze (RAM)

The RAM method was used to evaluate the impairment of hippocampus-dependent spatial memory. The procedure was conducted following a protocol described in one of our previous studies [5].

Statistical analysis

Statistical analysis was performed using SigmaStat® 11.0, applying one-way ANOVA, followed by post hoc Bonferroni test. The results are presented as mean±SEM. Cases with "p" values lower than 0.05 were accepted as statistically significant.

Results

We measured the anxiety levels by using EPM. The treatment with Aβ significantly decreased the number of entries into the aversive open arms of the EPM and the time spent inside of them ($p<0.01$). Agomelatine corrected anxiety behavior of Aβ-treated rats: the animals treated with both Aβ and Ago entered the open arms more often ($p< 0.01$) and spent significantly longer time ($p < 0.01$) there, as compared to the animals treated only with Aβ (Figure 2).

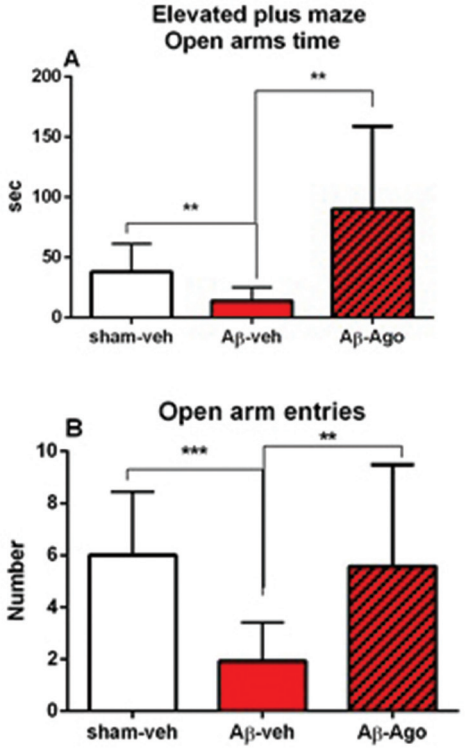

Figure 2. Anxiety level analysis by EPM

The results from the OF test confirmed our observations during the EPM test. The Aβ model was characterized by a decreased total activity and time in the central zone ($p<0.001$), while Ago alleviated the anxiety level in the OF test. The Aβ-Ago animals stayed longer in the center and showed a locomotor activity similar to that of the controls (Figure 3).

Rats with AD showed depressive-like behavior with higher immobility time in the FST than the sham-veh group ($p<0.001$). Agomelatine treatment exerted an antidepressant effect, decreasing the time spent in immobility (Figure 4).

Spatial representation is one aspect of cognition where the abilities of humans and animals have been extensively compared for decades. The number of working memory errors($p<0.05$) was estimated over five days of RAM training. Ago alleviated spatial memory impairment during the last session (Figure 5).

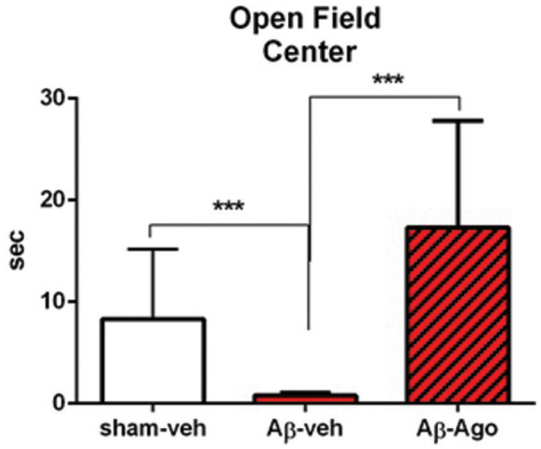

Figure 3. Locomotor activity and anxiety evaluation by OF test

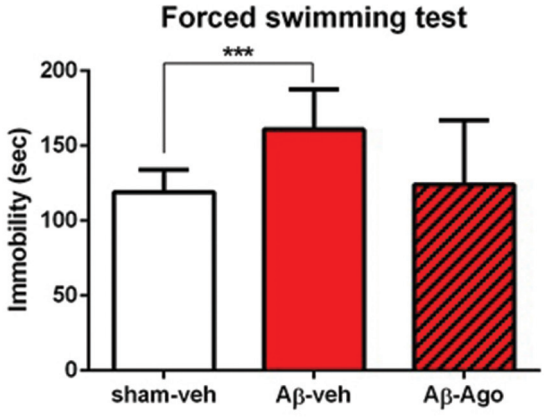

Figure 4. Forced swimming test showing more extended periods of immobility in Aβ rats

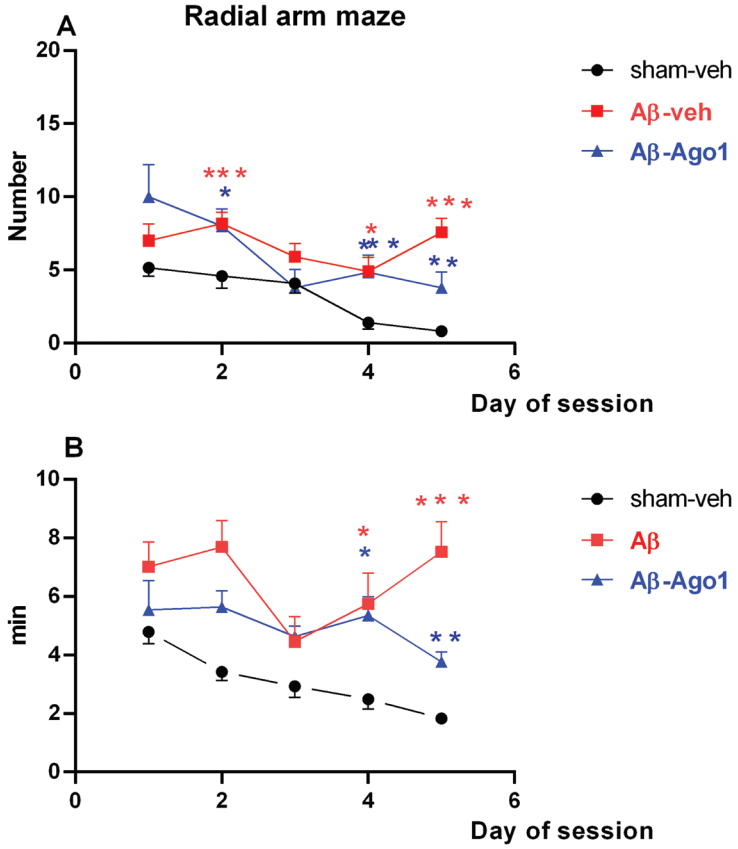

Figure 5. Increased number of working memory errors in the Aβ group, evaluated by the RAM test

Discussion

As seen by the results obtained by EPM, agomelatine corrected the anxiety-like behavior of Aβ rats as they entered the open arms more often and spent a significantly longer time there. During the OF test, our observations showed that the Aβ rats were characterized by decreased total activity and time spent in the central area. At the same time, Ago alleviated the levels of anxiety. Aβ-Ago animals stayed longer in the center and showed locomotor activity similar to the controls.

Agomelatine treatment exerted an antidepressant effect and decreased the immobility time. One aspect of cognition where the abilities of animals and humans have been extensively compared for decades is spatial representation. "Place cells" have been described in the rat hippocampus, suggesting that hippocampal lesions can impair spatial memory [13].

In accordance with the results we obtained from the streptozotocin-induced AD rat model [5], agomelatine proved to be sufficient for correction of depressive behavior in an Aβ-induced AD rat model. Agomelatine alleviated the anxiety levels (OF test, EPM, FS) and anhedonia (sucrose preference rate) caused by Aβ. This novel drug has the ability not only to exert antidepressant effects in animal and clinical studies. The drug can also synchronize the circadian rhythms and exert antidepressant effects in animal and clinical studies [11]. The agomelatine antidepressant action differs from other conventional antidepressant medications. It exerts its positive effect not only as a behavioral modulator but also alleviating the concentrations of different biochemical markers [12]. These findings indicate that agomelatine brings about more therapeutic effects than just amending the symptoms of depressive behaviour [12]. The specific properties of agomelatine may result from its action as an MT1/MT2 agonist and a 5-HT(2C) receptor antagonist. Multiple mechanisms are being proposed, showing that agomelatine is involved in neurogenesis and cell survival, activity-regulated cytoskeleton-associated protein (Arc) and glutamate secretion, and brain-derived neurotrophic factors (BDNF) secretion. Also, the medication significantly lowers serum and brain levels of pro-inflammatory cytokines, like interleukin (IL)-1β, TNFα, and brain levels of IL-6 [13].

Conclusions

Agomelatine has a beneficial influence on anxiety, emotional status, and spatial memory after icv injection of Aβ. Future biochemical and histological experimental studies will be carried out to ascertain that the icv Aβ injected rats react well to agomelatine treatment. Our findings suggest that chronic administration of agomelatine could alleviate the burden of AD and may be further tested as a promising pharmaceutical treatment of the disease.

Acknowledgements

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