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Agomelatine Protection in an LPS-Induced Psychosis-Relevant Behavior Model

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Background: The aim of this study was to investigate the effect of agomelatine in a psychosis-relevant behavior model.

Material/Methods: We used 18 adult male Wistar rats in this study. Twelve rats given LPS for endotoxemia were randomly divided into 2 groups (n=6). Group I was treated with 1 mL/kg 0.9% NaCl i.p. and Group II was treated with 40 mg/kg agomelatine. Six normal rats served as the control group and were not given LPS for endotoxemia. Cylindrical steel cages containing vertical and horizontal metal bars with top cover were used. Rats were put in these cages for the purpose of orientation for 10 min. Apomorphine was given to rats removed from cages, and then they were immediately put back in the cages for the purpose of observing stereotyped conduct. Brain HVA levels and plasma TNF-α levels were evaluated in tissue homogenates using ELISA. The proportion of malondialdehyde (MDA) was measured in samples taken from plasma for detection of lipid peroxidation similar to thiobarbituric acid reactive substances.

Results: LPS induced-plasma TNF-α, brain TNF-α, and plasma MDA levels were significantly lower in the LPS+agomelatine group compared to the LPS+saline group ($p<0.05$). HVA levels and stereotype scores were significantly lower in the LPS+agomelatine group compared to the LPS+saline group ($p<0.001$).

Conclusions: Agomelatine reduced TNF-α, HVA, MDA levels, and the stereotype score in relevant models of psychosis. Our results suggest that the anti-inflammatory effect of agomelatine involved oxidant cleansing properties and that its effects on the metabolism of dopamine can play an important role in the model of psychosis.

MeSH Keywords: Behavior, Animal • Psychotic Disorders • Stereotyped Behavior

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Background

The nervous system is sensitive to many factors and the resulting inflammatory response against sepsis affects brain functions. Sepsis can result in encephalopathy without causing any organ failure [1]. Sepsis-associated encephalopathy (SAE) may be caused by oxidative stress, increased proinflammatory cytokines and factors, and neurotransmitters changes [2,3]. Bacterial endotoxins, such as LPS, are the primary factors that cause severe inflammatory reactions in the body [1]. LPS is an inflammatory agent; in experimental animal models it has been shown to participate in death of nigrostriatal dopaminergic neurons and formation of parkinsonian symptoms [4]. LPS has been shown to cause pathological brain damage in the cortex, hippocampus, and striatum [5]. In the case of SAE, secreted proinflammatory cytokines, such as TNF-α, IL1B, and IL6, cause the disruption of the blood-brain barrier and effect the dopaminergic, Na, and serotonergic neurotransmission in the CNS, leading to cognitive impairment [6].

Melatonin is a hormone with free radical scavenging and antioxidant properties. It is secreted from the pineal gland and has an important role in the regulation of circadian rhythm, free radical cleaning, and antioxidant properties, and shows its effect through MT1 and MT 2 receptors. Melatonin plays an important role in the various neuropeptides and neurohormones that affect the immune system [7,8]. Agomelatine is a molecule that is an agonist to MT1 and MT2 receptors, with high affinity and antagonism to 5-HT2B and 5-HT2C receptors with moderate affinity [9]. Levels of dopamine and noradrenaline are increased by agomelatine except for alteration of serotonin proportion [10]. In addition to the neuroendocrine functions of melatonin, it also shows similar psychotropic effects, including sedative, analgesic, anticonvulsant, hypnotic, and anxiolytic effects in animal studies [11]. It has been shown that administration of melatonin in rats increases GABA levels in the cerebellum and cerebral cortex [12]. The present study aimed to investigate the effect of agomelatine in a psychosis-relevant behavior model in rats.

Material and Methods

Animals

The experimental protocol was approved by the Institutional Animal Care and Ethics Committee of Gaziosmanpasa University. We used a total of 18 albino male Wistar rats weighing 220–240 g. All animals were housed in cylindrical steel cages with a temperature of 22±2°C and a 12-h light/dark cycle. Rats were provided a standard diet of rodent chow and water ad libitum. All experimental processes were carried out from 10:00 to 16:00 in the light cycle. The experimental protocol performed in the study was approved by the Institutional Animal Care and Ethics Committee of Gaziosmanpasa University.

Chemicals

All drugs were freshly prepared. Apomorphine hydrochloride (Sigma Chemical Co., St. Louis, MO) was dissolved in saline containing 0.1% ascorbic acid prior to experiments. Agomelatine (Valdoxan, Servier Drug Company) was dissolved in saline. Saline (0.9% NaCl) was used as the control solution. All solutions were injected intraperitoneally (i.p.) with a volume of 1 mL/kg body weight.

Endotoxemia

Twelve rats received a dose of endotoxin at time 10:00) (1 mg/kg, i.p., *Escherichia coli* LPS 026 B6; SIGMA, St. Louis, MO).

Apomorphine-induced stereotypic behavior test

Mesolimbic and nigrostriatal dopaminergic pathways play important roles in the mediation of locomotor activity and stereotyped behavior. Because of the excitation of dopamine receptors, apomorphine-induced stereotypy has been used as an appropriate method for *in vivo* scanning of dopamine agonists or antagonists and assessment of dopaminergic activity [13,14].

Because we aimed to assess the effect of agomelatine on behavioral stereotypy in early endotoxemia, we conducted an apomorphine-induced stereotypic behavior test in the first 8 hours of endotoxemia. Assessment of stereotyped behavior was done by 2 observers blind to the study groups. All experimental processes were carried out between time 10:00 and 16:00. For orientation, all rats were kept for 10 min in 18×19 cm cylindrical steel cages with vertical (1 cm apart) and horizontal (4.5 cm apart) metal bars 2 mm in size, with a top cover.

The 12 rats given LPS for endotoxemia (at time 10: 00) were randomly divided into 2 groups (n=6): Group I was treated with 1 mL/kg 0.9% NaCl i.p. and Group II was treated with 40 mg/kg agomelatine (Valdoxan, Servier Drug Company). Six normal rats served as the control group and were not given LPS for endotoxemia. Then, for orientation, rats were kept for 10 minutes in 18×19 cm cylindrical steel cages that had vertical (1 cm apart) and horizontal (4.5 cm apart) metal bars 2 mm in size with a top cover.

Apomorphine was given to rats removed from cages at time 16:00, then rats were immediately put in cages for the purpose of observing stereotyped behavior. Signs of stereotypy, which mainly include sniffing and gnawing, were observed and scored as follows: absence of stereotypy (0), occasional sniffing (1), occasional sniffing with occasional gnawing (2),

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frequent gnawing (3), intense continuous gnawing (4), and intense gnawing and staying in the same location (5). The stereotypic behavior was rated after each minute, and the mean of a 15-min period was calculated and recorded (15).

Obtaining plasma and tissue samples

A combination of ketamine hydrochloride at a dose of 50 mg/kg and xylazine hydrochloric at a dose of 7 mg/kg was injected intraperitoneally to study group rats. Blood samples were taken from cardiac tissue with a 1-ml syringe and placed into tubes including heparin. Then, at 3000 rpm and at room temperature, they were centrifuged for 10 minutes and stored at -80°C until analysis. After decapitation, brains were rapidly removed and stored at -80°C until biochemical measurement.

Assessment of brain HVA level

An enzyme-linked immuno-sorbent assay (ELISA) kit (Cusabio Biotech Co., LTD) was used to quantify brain HVA levels in tissue homogenates. In accordance with the manufacturer's protocol, HVA levels in supernatants were detected in duplicate. The determination range was between 0.312 ng/ml and 20 ng/ml for HVA assay. The Bradford method was used for protein concentration of the brain homogenates [16].

Assessment of plasma TNF-α level

A commercially available ELISA kit (eBiosciences) was used for the measurement of plasma TNF-α level. The plasma samples were diluted to 1: 2 and TNF-α was determined in duplicate tubes in accordance with the manufacturer's instructions. The detection range was 16-2000 pg/ml. Intraassay and interassay coefficients of variation were less than 10% in each determination.

Assessment of lipid peroxidation

The proportion of malondialdehyde (MDA) was measured in samples taken from plasma for detection of lipid peroxidation similar to thiobarbituric acid reactive substances. Briefly, trichloroacetic acid and TBARS reagent were added to the plasma samples, then mixed and incubated at 100°C for 60 min. After cooling on ice, the samples were centrifuged at 3000 rpm for 20 min and the absorbance of the supernatant was read at 535 nm. Tetraethoxypropene was used for calibration and MDA levels were expressed as nM [17].

Invention of TNF- α in Brain Tissue

Brain tissue stored at –80°C was homogenized with a glass homogenizer in 1 ml of buffer including 1 mmol/L of PMSF, 1 mg/L of pepstatin A, 1 mg/L of aprotinin, and 1 mg/L of leupeptin in PBS solution (pH 7.2). After homogenization, samples were centrifuged at 12 000 rpm for 20 min at 4°C, then supernatant was collected. Total protein was detected using the Bradford method. An ELISA kit (eBioscience, Inc, San Diego, CA) specific for rats was used for the measurement of the level of TNF in the tissue supernatants. The measurement of TNF-α was performed in a stepwise fashion consistent with the protocol of the ELISA kit. According to the specifications given by the manufacturer, the inter-assay and intra-assay coefficients of variation for TNF-α were 7.9–8.2% and 6.1–6.5%, respectively. Thirty pg/ml was determined as the minimum limit of TNF-α detected for this assay. The cytokine contents in the brain tissue are expressed as nanograms of cytokines per gram of protein.

Statistical analysis

SPSS version 15.0 for Windows was used for data analyses. Student's t test and analysis of variance (ANOVA) were used for the purpose of comparing the groups of parametric variables. The Mann-Whitney U test was used for comparing the groups of nonparametric variables. According to analyses of outcomes, mean ± standard error of mean (SEM) was obtained. A value of $p<0.05$ was regarded as statistically significant.

Results

In this study LPS-induced plasma TNF-α, brain TNF-α, and plasma MDA levels were found to be significantly lower in the LPS + agomelatine group compared to the LPS + saline group ($p<0.05$). HVA levels and stereotypy scores were significantly lower in the LPS + agomelatine group compared to the LPS + saline group ($p <0.001$) (Table 1; Figures 1–3).

Discussion

In this study, lipid peroxidation products of MDA levels were found to be increased as a result of LPS and apomorphine, and were significantly reduced after treatment with agomelatine. It has been reported that 6-OHDA, which is a neurotoxin, causes neuronal death via oxidative radicals [18]. In schizophrenia, in studies considering oxidative metabolism, generally oxidants has been reported to increase and it has been reported that oxidative stress may play a role in the pathophysiology of schizophrenia [19,20]. In a meta-analysis in which MDA levels of schizophrenia patients examined, MDA levels were reported to be higher [21]. In another meta-analysis, TBARS levels were shown to higher in patients with schizophrenia [22]. Due to the potential role of oxidative stress in the pathophysiology of schizophrenia, the effects were used in the treatment of schizophrenia on oxidative metabolism examined in some studies. However, the results of studies that examined effects

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Table 1. HVA levels and stereotypy scores in LPS + agomelatine and LPS + saline groups.

	Stereotype score	HVA (pg/μg)
Control	2.7±0.22	1.18±0.10
LPS + saline	3.75±0.1*	3.73±0.30#
LPS + agomelatine	0.93±0.08**	1.30±0.14**

Data are expressed as mean ±SEM. Statistical analyses were performed by the Kruskal-Wallis variance analysis and the Mann-Whitney U-test. * p<0.001; # p<0.000 (different from control); ** p<0.000 (different from LPS + saline).

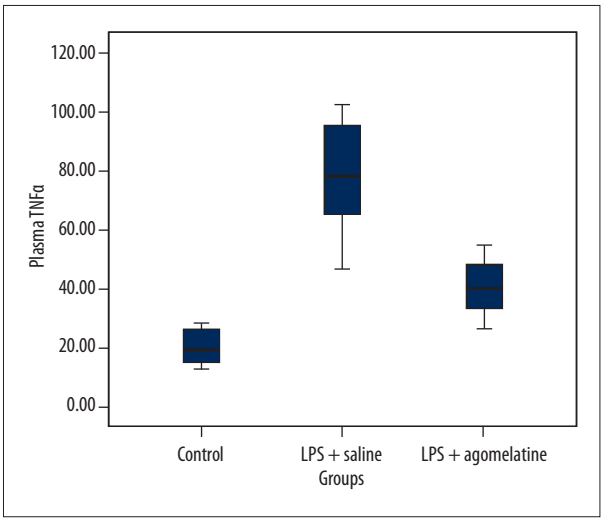

Figure 1. Plasma TNF-α levels in groups.

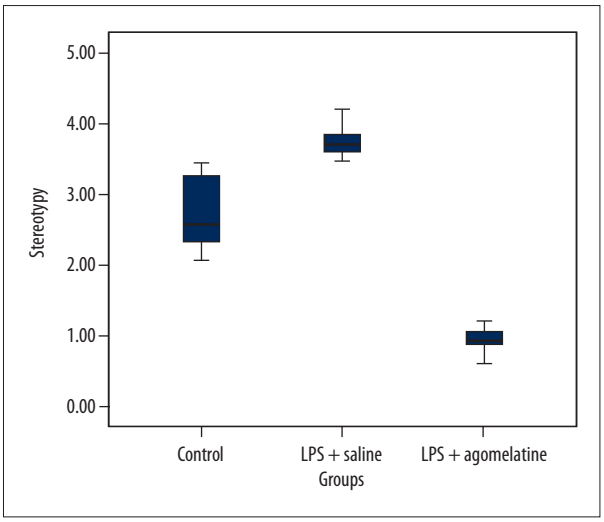

Figure 2. Plasma stereotype scores in groups.

of antipsychotics used to treat schizophrenia on oxidative metabolism are controversial [23]. A growing body of evidence suggests that typical antipsychotics increase oxidants and decrease antioxidants [24,25]. In studies of atypical antipsychotics, oxidants increased and antioxidants decreased, but other studies have shown the opposite effect [26–31]. In newly

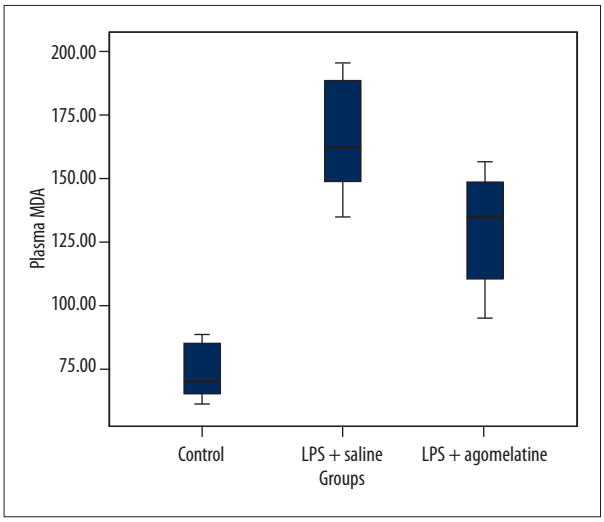

Figure 3. Plasma MDA levels in groups.

diagnosed patients with schizophrenia after treatment with AAP, significant reductions in MDA levels were reported [32]. In an independent study, agomelatine was shown to reduce levels of TBARS and to have antioxidant activity in a strychnine-induced seizure model [33]. In our study model, decline of increasing MDA levels suggested that agomelatine may recover psychotic symptoms via its regulatory effect on oxidative stress. In addition to LPS-induced psychosis-relevant behavior, increased levels of TNF-α were also found to be decreased after agomelatine treatment [34–36]. TNF-α increases in the circulation after LPS administration and is a key mediator playing a role in SAE formation [37,38].

TNF-α stimulates oxidative burst in neutrophils. In a meta-analysis in which cytokines in patients with schizophrenia were examined, TNF-α levels were found to be increased in cases of first-episode schizophrenia and acute attack of schizophrenia. In addition, TNF-α was suggested as a trait marker for schizophrenia [39]. The antipsychotics haloperidol, risperidone, quetiapine, and aripiprazole have been shown to inhibit TNF-α production4[40–43]. In another study, risperidone have been shown to increase TNF-α levels [44]. The results of studies examining changes in cytokines AP after treatment are contradictory. Some studies showed that cytokines increased AP after treatment, some

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studies showed decreased levels of cytokines, and some found that levels of cytokines were not altered [45]. In the inflammatory state in psychotic symptoms and possible anti-inflammatory effects of antipsychotics, inflammation has become a therapeutic target in the treatment of psychosis [45,46]. Agomelatine decreases the levels of cytokines such as TNF-α and IL-6, and by displaying antioxidant activity reverses paracetamol-induced hepatotoxicity, thus showing protective effects for the liver [47]. In our study, the reduction in the levels of TNF-α via agomelatine indicates that agomelatine may have anti-inflammatory properties and can have beneficial effects in schizophrenia treatment. HVA is a terminal metabolite of DA and serotonin in the brain [48]. In a study of schizophrenia patients treated with AAP, HVA levels were found to be increased after treatment [49]. In the same study, a positive correlation was found between HVA level and PANSS positive subscale [50]. Plasma HVA levels were found to associate with psychotic symptoms. In risperidone-treated acute schizophrenia patients who respond to treatment, plasma HVA levels decreased, but were not decreased in patients who do not respond to treatment. It was also reported that high HVA level before switching may predict good response to the second-line antipsychotics after unsuccessful first antipsychotic treatment [51]. In another study, plasma HVA levels were shown to be significantly decreased in risperidone-, olanzapine-, and aripiprazole-treated schizophrenia patients [52]. Plasma HVA levels decreased in the first week of treatment and were correlated with good prognosis [53,54]. In several studies, HVA levels were reported to be positively correlated with clinical improvements in schizophrenia [50]. In our study, agomelatine significantly decreased HVA levels in the group treated with agomelatine and it was also found that psychotic-like behavior significantly decreased. This can be considered as an API-like effect of agomelatine.

Conclusions

We showed that agomelatine reduced TNF-α, HVA, and MDA levels, as well as the stereotype score in relevant models of psychosis. Our results suggest that the anti-inflammatory effect of agomelatine involves oxidant-cleansing properties and that its effects on the metabolism of dopamine can play an important role in the model of psychosis.

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