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Research / Araştırma

Antipsychotic-Like Effect of Agomelatine in a Rodent Model

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ABSTRACT

Antipsychotic-like effect of agomelatine in a rodent model

Objective: Agomelatine is a naphthalene bioisostere of melatonin. Melatonin is involved in several neurophysiological systems; nevertheless, data about the relationship between melatonin and psychosis such as schizophrenia are limited and contradictory. In this study, we examined the antipsychotic-like effects of agomelatine in a rodent model.

Method: In this study, we evaluated the effect of agomelatine on novelty-induced rearing behavior and apomorphine-induced stereotypical behavior in male rats. Agomelatine (20 and 40mg/kg, i.p.), chlorpromazine (1mg/kg, i.p.), or isotonic NaCl (1mL/kg, i.p.) were administered to four groups of rats (n=6), respectively. An hour later, apomorphine (2mg/kg, s.c.) was administered to each rat.

Results: Our results showed that either dose of agomelatine decreased rearing behavior in rats significantly, in a dose dependent manner. Agomelatine also decreased the stereotypical behaviour scores like chlorpromazine did.

Conclusion: We conclude that agomelatine has beneficial effects on rearing and stereotypical behaviour, which were accepted to be indicators of antipsychotic effect.

Key words: Agomelatine, apomorphine, psychosis

ÖZET

Bir kemirgen modelinde agomelatinin antipsikotik benzeri etkisi

Amaç: Daha önce yapılmış çalışmalarda agomelatinin nörofizyolojik sistemler üzerine olan etkileri gösterilmiştir, ancak bazı psikoz modelleri üzerine olan etkisi net değildir. Bu çalışmada agomelatinin sıçanlarda oluşturulan stereotipik hareketleri üzerine olan etkilerini incelemeyi amaçladık.

Yöntem: Çalışmamızda erkek sıçanlarda apomorfinle indüklenen stereotipik hareket skorlaması değerlendirildi. Bu çalışmaya 4 grup alındı (n=6), 1. Grup 20mg/kg melatonin, 2. Grup 40mg/kg melatonin, 3. Grup 1mg/kg klorpromazin, 4. Grup izotonik 1 mL/kg alacak grup olarak belirlendi. Belirtilen ajanlar i.p olarak uygulandıktan 1 saat sonra sıçanlara apomorfin (2mg/kg, s.c.) uygulanarak indükte stereotipi skorları ve lokomotor aktiviteler değerlendirildi.

Bulgular: Sonuçlarımız göstermektedir ki agomelatin, lokomotor aktivite ve stereotipi skorlarını istatistiksel olarak anlamlı derecede azaltmaktadır, üstelik bu durum doz artışıyla belirginleşmektedir.

Sonuç: Agomelatinin steriotipi ve lokomotor aktiviteler gibi psikotik belirtiler üzerine olumlu etkilerinin olabileceği düşünülebilir.

Anahtar kelimeler: Agomelatin, apomorfin, psikoz

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INTRODUCTION

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone synthesized in the brain by the pineal gland from the amino acid tryptophan. Synthesis and release of melatonin are enhanced by darkness and suppressed by light, suggesting the involvement of melatonin in circadian rhythms and regulation of diverse body functions (1). It acts through G-protein-coupled membrane receptors, MT1 and MT2 (2). Melatonin treatment may have some beneficial effects in the treatment of mental disturbances (2) due to its anti-inflammatory (3) antinociceptive (4), anxiolytic (5), chemical detoxification properties (6) and its protective effects against oxidative stress (7,8). Agomelatine, a naphthalene bioisostere of melatonin, which is a potent

MT1 and MT2 agonist and 5-HT(2C) receptor antagonist, has also been found effective in the treatment of depressive and anxiety symptoms associated with major depression (9).

Schizophrenia is one of the most severe neurodevelopmental psychiatric disorders with an incidence of approximately 1% in the population. Dopaminergic, serotonergic and glutamatergic dysfunctions are known to be involved in the etiopathology of schizophrenia. One of the oldest models of schizophrenia is based on the observation that serotonergic hallucinogens can provoke a 'model psychosis' in normal humans (10). Involvement of the serotonergic system in the pathophysiology of schizophrenia was suggested in the 1950s. This suggestion was based on observations with lysergic acid diethylamide (LSD), which affect serotonergic transmission (11). Stoll confirmed that LSD produced mescaline-like effects, but was much more potent, and found that the effects of LSD resemble the symptoms of schizophrenia (12). LSD and 5-HT have a similar chemical structure. One of the strongest arguments for the involvement of 5-HT in schizophrenia was the discovery of atypical antipsychotics such as clozapine, risperidone, and olanzapine, which act in part by blocking 5-HT2 receptors with some selectivity over the dopamine (DA) D2 receptor (13). Animal studies indicate that selective 5-HT2A antagonists have antipsychotic-like effects (14).

The role of melatonin in schizophrenia has been mentioned in a number of studies; some results are contradictory, and the therapeutic potential of melatonin in schizophrenia is not clear. It has been suggested that pineal calcification may be responsible for the disturbance of melatonin, which appears to be a non-genetic factor in schizophrenia associated with perinatal injury (15,16).

It has been suggested that lower levels of melatonin in schizophrenic patients may be related to the schizophrenic process itself (17). Bersani et al. (18) confirmed the lack of a characteristic circadian pattern of melatonin secretion in patients with schizophrenia. Thus, it has recently been hypothesized that schizophrenia may be a disorder involved in a possible dysfunction of the suprachiasmatic nucleus (SCN) (19). Moreover, a single nucleotide polymorphism (SNP) in the promotor of melatonin receptor 1A gene is significantly associated with schizophrenia and insomnia symptoms seen in schizophrenia patients (20). A recent review on the interaction between schizophrenia and melatonin can be found in the literature (21).

When the recent literature is examined, we see that schizophrenia appears to be associated with reduced melatonin levels. It could be expected that melatonin treatment may have some beneficial effects on schizophrenia. However, clinical and experimental reports have shown that the effects of melatonin on the signs of schizophrenia are very limited. These studies are mostly focused on the interaction between melatonin and antipsychotic drugs or the potential immunomodulatory effect of melatonin (2). In this respect, the therapeutic potential of melatonin in schizophrenia is not clear. In this study, we examined antipsychotic-like effects of agomelatine in a rodent model.

METHOD

Animals and Housing Conditions

Twenty-four adult male Sprague Dawley rats (220-240g) were included in the study. All animals were kept under a standard 12h light/dark cycle in a temperature-controlled (22±2°C) environment with ad libitum access to rodent chow. All experimental procedures were performed during the light phase (from 10:00 to 16:00). The experimental protocol performed in the study was approved by the Institutional Animal Care and Ethics Committee of Gaziosmanpasa University.

Drugs

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 control solution. All solutions were administered intraperitoneally (i.p.) at a volume of 1mL/kg body weight.

Assessment of Novelty-Induced Rearing Behavior

Novelty- induced rearing behavior is used to assess the central excitatory locomotor behavior in rodents (22). Four groups of rats (n=6) were administered agomelatine (20 and 40mg/kg, i.p.), chlorpromazine (1mg/kg; i.p.), or isotonic NaCl (1mL/kg, i.p.) respectively. An hour later, novelty-induced rearing behavior was explored after transferring the animals directly from their home cages to a transparent Plexiglas cage (45cmx25cmx25cm). The rearing frequency (number of times the animal stood on its hind limbs or with its fore limbs against the walls of the observation box or free in the air) was recorded for 10min. All rats were monitored individually by two observers, who were blinded to the study groups. The arena was cleaned with 5% alcohol to eliminate olfactory bias before beginning to observe the next animal.

Apomorphine-Induced Stereotypical Behavior Test

The mesolimbic and nigrostriatal dopaminergic pathways play crucial roles in the mediation of locomotor activity and stereotypical behavior. Apomorphine-induced stereotypy is due to the stimulation of dopamine receptors and has been used as a convenient method for in vivo screening of dopamine agonists or antagonists and assessment of dopaminergic activity (23,24). Briefly, four groups of rats (n=6) were administered agomelatine (10 and 20mg/kg, i.p.), chlorpromazine (1mg/kg, i.p.), and isotonic saline (1mL/kg, i.p.) respectively. An hour later, apomorphine (2mg/kg, s.c.) was administered to each rat. First, as an orientation period, the rats were placed for 10 minutes into cylindrical metal cages (18x19cm) consisting of vertical (1cm apart) and horizontal (4.5cm apart) metal bars (2mm) with an upper lid. After apomorphine administration, the rats were immediately placed back into the metal cages and observed for stereotypical behavior. Signs of stereotypy, which include mainly sniffing and gnawing were observed and scored as follows: absence of stereotypy (0), occasional sniffing (1), occasional sniffing with occasional gnawing (2), frequent gnawing (3), intense continuous gnawing (4), and intense gnawing and staying on the same spot (5). The stereotypical behavior was rated after each minute, and a mean for a 15min period was calculated and recorded (25).

Statistical Analysis

Statistical evaluation was performed by one-way analysis of variance (ANOVA). Post hoc Bonferroni test was used to identify differences between the experimental groups. Results are presented as mean±SEM (standard error of mean). A value of $p<0.05$ was considered significant.

RESULTS

The Effect of Agomelatine on Novelty-Induced Rearing Behavior

Figure 1 represents the effects of agomelatine and chlorpromazine treatment on rearing behavior. When the 20 and 40mg/kg agomelatine groups were compared with the saline group, the agomelatine groups had lower scores ($p<0.001$). When the 20 and 40mg/kg agomelatine groups were compared with the chlorpromazine group (1mg/kg), the chlorpromazine group's scores were lower than either of the agomelatine groups'. When the two groups of receiving (20mg/kg and 40mg/kg) were compared, there was no significant difference (Figure 1).

The Effect of Agomelatine on Apomorphine Induced Stereotypical Behavior Test

Figure 2 represents the effects of agomelatine and chlorpromazine treatment in the Apomorphine-Induced Stereotypical Behavior Test. When the 20 and 40mg/kg

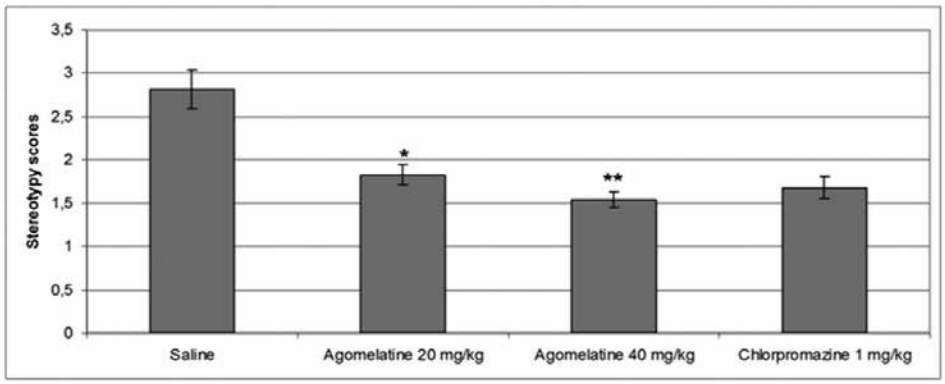

Figure 1: Apomorphine-induced stereotypy scores. Data are expressed as mean±SEM. Statistical analysis was performed by oneway analysis of variance (ANOVA) and Bonferroni's post hoc test.

*Agomelatine (20mg/kg) < Saline (p<0.01, statistically significant), **Agomelatine (40mg/kg) < Saline (p<0.001, statistically significant)

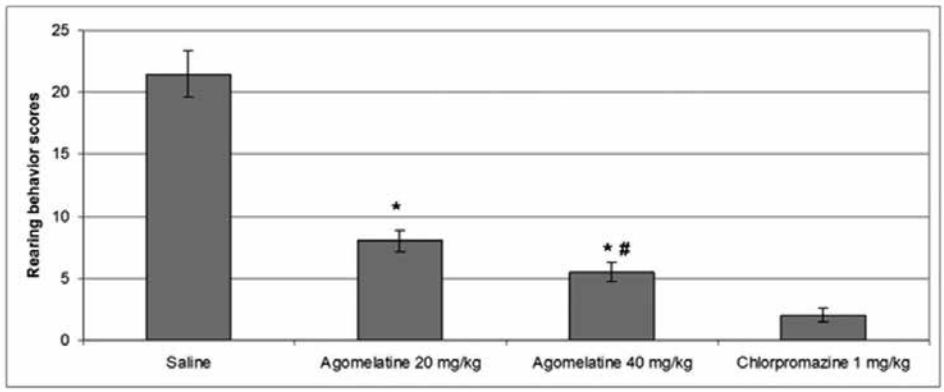

Figure 2: Rearing behavior scores. Data are expressed as mean±SEM. Statistical analysis was performed by one-way analysis of variance (ANOVA) and Bonferroni's post hoc test.

*Agomelatine (20 and 40mg/kg) < Saline (p<0.001, statistically significant), #Chlorpromazine < Agomelatine (20 and 40mg/kg) (p<0.05, statistically significant)

agomelatine groups were compared with the saline group, the agomelatine group had lower scores (p<0.01, p<0.001). When the 20 and 40mg/kg agomelatine groups were compared with the chlorpromazine group (1mg/kg), there was no significant difference (p>0.05). When the comparison was made between the two groups of agomelatine (20mg/kg and 40mg/kg), there was no significant difference (p>0.05) (Figure 2).

DISCUSSION

The results of this study clearly showed that agomelatine is effective on rearing behavior and stereotypy, which are accepted to be indicators of an anti-psychotic effect. Theoretically, the anti-psychotic effect is mediated by means of antidopaminergic activity in certain regions of the central nervous system. Some evidences suggest that melatonin modulates the striatal and limbic activity (26). Melatonin-binding sites have been found in some brain areas such as the striatum and the limbic system, which have rich dopamine content (26). It has also been hypothesized that melatonin inhibits the limbic dopaminergic activity, thus mesolimbic and mesocortical dopamine tone may increase when the melatonin secretion decreases (15,27). These data imply that melatonin may be

essential in the adjustment of the dopaminergic activity in some brain areas. Thus, as a result of the decreased melatonin secretion during puberty, mesolimbic dopaminergic tone may be excessively increased, and its effect could be responsible in part for triggering the emergence of schizophrenia signs during adolescence (15). Apomorphine-induced stereotypy scores and rearing behavior scores significantly declined when compared with saline in a dose-related manner. The 40mg/kg agomelatine administration has similar effects with chlorpromazine on apomorphine-induced stereotypy scores, however it is not as efficient as 40mg/kg melatonin. In addition, 20mg/kg agomelatine has antipsychotic-like effects too. Chlorpromazine, a very effective antagonist of D2 dopamine receptors, exerts additional antiadrenergic, anticholinergic, and antihistaminergic effects (28). Hence, the efficacy of chlorpromazine on rearing behavior may be associated with its sedative effect, which is mainly attained by anticholinergic and antihistaminergic properties of that drug.

These findings show us that agomelatine was decreasing the dopamine secretion in mesolimbic and nigrostriatal dopaminergic pathways. Our study supports the study performed by Bersani et al., which suggested that lover levels of melatonin in schizophrenic patients may be related to the schizophrenic process itself (18).

The dopaminergic hypothesis fails to fully explain the complex etiopathogenesis of schizophrenia. Dysfunctions in the serotonergic and glutamatergic neurochemical systems have also been implicated. Investigators hypotheized that the kynurenine pathway may partially serve to integrate these apparently disparate findings (29,30). This highly regulated pathway is responsible for the metabolism of approximately 80% of the non-protein-bound tryptophan, the essential amino acid needed for the synthesis of serotonin (31). Metabolites of this pathway including the neurotoxic quinolinic acid and the neuroprotective kynurenic acid, are collectively known as kynurenines. Kynurenic acid is a non-selective antagonist of excitatory amino acid receptors with a high affinity for the glycine co-agonist site of the N-methyl-D-aspartate (NMDA) receptor that mediates glutamatergic hypofunction (32,33). Conversely, quinolinic acid is an NMDA receptor agonist. NMDA receptor hypofunction is thought to be responsible for the pathogenesis of schizophrenia (28). Investigators have reported significantly elevated kynurenine and kynurenic acid levels in the frontal cortex of patients with schizophrenia (34). Both clinical and preclinical studies suggest that agomelatine affects trypthophan catabolism and kynurenine pathway. By preventing the increase of kynurenine-3-monooxygenase (KMO) and kynurenine aminotransferase (KAT)-II that are acting on kynurenine, it may switch the path toward neurotoxic or neuroprotective arms, respectively (35-37). Consequently, agomelatine reduces kynurenine, which is increasing in schizophrenia.

Melatonin also interacts with the serotonergic 5-HT2 receptors and in pharmacological doses, it acts as a 5-HT2 receptor antagonist. Moreover, it has been suggested that the chronic administration of melatonin-enhancing agents in conjunction with atypical antipsychotics could augment their effects on the negative symptoms of schizophrenia (38). Many atypical antipsychotic agents such as clozapine, olanzapine, risperidone and quetiapine also block 5-HT2 receptors and there is a link between their antipsychotic activity and 5-HT2 blocking activity (39,40).

In conclusion, our results produce strong evidence about a potential antipsychotic effect of agomelatine because of its anti-dopaminergic nature. In addition, agomelatine affects kynurenine pathway that is related to the glutamatergic system.

We could not quantify and evaluate brain neurotransmitter levels; that was the most important limiting factor of our study. So, this study should be supported by further experimental and clinical research.

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