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The Effect of Agomelatine on the Nociceptive System

Yuksel Kivrak[1], Basaran Karademir[2], Hayati Aygun[3], Yusuf Ersan[4], Mustafa Ari[5], Elif Karaahmet[6], Ibrahim Yagci[7]

ÖZET:

Agomelatinin nosiseptif sistem üzerine etkisi

Amaç: Bu araştırmanın amacı bir antidepresan olan agomelatinin nosiseptif sistem üzerindeki etkisini ortaya çıkarmaktır.
Yöntem: Bu amaçla, 24 Swiss albino erkek fare (4 aylık ve 28.8±1.18 g ağırlığında) random olarak eşit sayıda farelerden oluşan üç gruba, A Grubu, B Grubu ve kontrol grubu olan C Grubu olarak ayrıldı. A Grubu'na 12.5 mg/kg agomelatin, B Grubu'na 25 mg/kg agomelatin ve C Grubu'na salin intraperitoneal yol ile verildi. Nosiseptif etkiyi değerlendirmek için hot plate metodu (50ºC) kullanılarak kontrol ve agomelatin gruplarına ait ağrı eşik değerleri 30. ve 60. dakika bulguları olarak kaydedildi.
Bulgular: Ağrı eşiği sonuçlarına göre agomelatin gruplarına ait veriler her iki zamanda da kontrol grubundan daha yüksek olarak bulundu. 30. dakika ölçümlerinde B grubu ile diğer gruplar arasında anlamlı farklılık gözlendi (p=0.007). Aynı zamanda grupların zamanla etkileşiminde de anlamlılık gözlendi (p=0.036).
Sonuçlar: Bu çalışmanın sonuçları agomelatinin farelerde nosiseptif sistem üzerinde analjezik etkinliğinin olabileceğini ortaya koymaktadır.

Anahtar sözcükler: agomelatin, analjezi, antidepresan, hiperaljezi, melatonin, nosiseptif sistem, ağrı

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ABSTRACT:

The effect of agomelatine on the nociceptive system

Objective: The aim of the study was to study the effects of agomelatine, an antidepressant, on the nociceptive system.
Methods: Twenty four male Swiss albino mice (four months old and 28.8±1.18 g average weight) were randomly divided into three groups, which were equal in numbers; Group A and B were the experimental groups and group C was the control group. Group A was given 12.5 mg/kg of agomelatine, Group B was given 25 mg/kg agomelatine and Group C was given physiological saline via intraperitoneal injection. To evaluate the nociceptive effects, by using the hot plate method (50ºC), pain threshold values of the control and agomelatine groups were recorded as the 30th and 60th minute findings.
Results: According to the pain threshold results, the datafor the two agomelatine groups were found to be higher than control group at both time points. In 30th minute measurements, between Group B and the other groups, significant differences were observed (p=0.007). In addition, significance in the interaction between time and group was observed (p=0.036).
Conclusions: The results of the study suggest that agomelatine might have analgesic efficacy on the nociceptive system in mice.

Keywords: agomelatine, analgesia, antidepressant, hyperalgesia, melatonin, nociceptive system, pain

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[1]Assist. Prof., [7]M.D., Kafkas University School of Medicine, Department of Psychiatry, Kars - Turkey
[2]Assist. Prof., Kafkas University Faculty of Veterinary Medicine, Kars - Turkey
[3]Assist. Prof., Kafkas University School of Medicine, Department of Orthopedics and Traumatology, Kars - Turkey
[4]PhD., Kafkas University Faculty of Science and Art, Department of Biology, Kars - Turkey
[5]Assist. Prof., Mustafa Kemal University School of Medicine, Department of Psychiatry, Hatay - Turkey
[6]Assist. Prof., Canakkale Onsekiz Mart University School of Medicine, Department of Psychiatry, Canakkale - Turkey

Corresponding author:
Dr. Yuksel Kivrak,
Kafkas Universitesi Tip Fakultesi, Psikiyatri Anabilim Dalı, Kars - Turkey

E-mail address:
ykivrak21@gmail.com

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INTRODUCTION

Depression is a multi-dimensional situation containing depressive mood, psychomotor disorders, sleep disorders, somatic, pain, and anxiety symptoms[1]. This presentation may be affected by age and sex[2]. It has been claimed that this condition will would be the second most prevalent after cardiovascular disorders in human health in the near future[3]. The life time prevalence of depression in Europe has been reported to be 14%[4]. According to "The national disease burden and cost-effectiveness study" depression is the 4th cause of disease burden in Turkey[5]. Moreover, one third of major depressive disorder patients do not respond to treatment[6].

Pain is the most common presenting somatic symptom in medical outpatients[7]. However in patients with depression, unexplained painful physical symptoms or medically unexplained pain complaints are common[8]. On average, 65% of patients with depression experience one or more pain complaints, and depression is present in 5% to 85% (depending on the study setting) of patients with pain conditions[9].

In the past, tricyclic antidepressants were used in patients reporting painful physical symptoms or to relieve organic pain, like neuropathic pain. They have been often prescribed in patients with painful conditions without depressive symptoms[10]. In the meantime there is a growing body of evidence that double acting antidepressants (Selective Norepinephrine Reuptake Inhibitors - SNRIs) and dopaminergic substances have higher efficiency in relieving painful symptoms (of organic origin or unexplained) with or without depression[11]. Among them duloxetine, venlafaxine, mirtazapine, milnacipran, bupropion, and tetracyclic antidepressants as well as MAO inhibitors are recommended for this treatment[12].

Antinociceptive actions of melatonin (MT) have been well demonstrated in a number of animal studies by using different types of models including acute pain, inflammatory pain and neuropathic pain[13]. Not only melatonin but also melatonin agonists such as 2-bromomelatonin[14], 6-chloromelatonin[15] and certain other pyrrolol indole derivatives of melatonin also exert significant anti-inflammatory and analgesic activity[13]. In this context, it has been suggested that the novel melatonergic antidepressant agomelatine might have a promising role in treating neuropathic pain associated with inflammation and nerve injury[13].

Agomelatine (N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide, S-20098) is a new drug entering psychiatric practice as antidepressant which is analog of melatonin (MT)[16]. It is a selective agonist of MT_1 and MT_2 receptors like melatonin, but additionally has antagonist effect on 5-hydroxytryptamine 2B and 2C ($5\text{-}HT_{2B}$ and $5\text{-}HT_{2C}$) receptors[17]. It is known that activation of 5-HT receptors leads to hyperalgesia[18]. Melatonin and some antidepressants (mianserin, mirtazapine, and amitriptyline) have antagonist effects on $5\text{-}HT_{2C}$ receptors and also have analgesic effect[17,19]. Nevertheless, no information about the nociceptive effect of agomelatine was found in the literature. The aim of this study was to determine the possible effect of agomelatine on the nociceptive system.

METHODS

The study was approved by the Ethics Committee of Kafkas University (Approval No. 2012-27).

Animals: Twenty-four healthy male, Swiss albino mice, (aged 4 months old and 28.8±1.18 g weight) were used in this study. The animals were placed in a room with a uniform warm (20-21^{0}C) temperature and a 12 hour light-dark cycle.

Hot Plate Test: This method has previously been used in similar research[20-25]. The animals were placed on the hot plate, which was in an open glass cylinder whose dimension was 17x20 cm. The temperature of the plate was adjusted to 50^{o}C. When the animal was placed on the plate surface, the test was started and then the reaction time was measured (hind paw licking or jumping). The surface was cleaned after each measurement with 20% of ethanol. The animals were kept on the plate for a maximum 45 seconds to avoid from the heat damage. Thus, values over 45 seconds were regarded as 45 seconds.

Procedure: The animals were divided into three equal groups (Control, Group A and B) randomly. Agomelatine was given via intraperitoneal injection (i.p.) to groups A and B (0.3 ml, 12.5 mg/kg and 0.3 ml, 25 mg/kg respectively) and 0.3 ml saline solution was given via the i.p. route to the control group. Because of a lack of studies on the effects of agomelatine on the nociceptive system in the literature, those

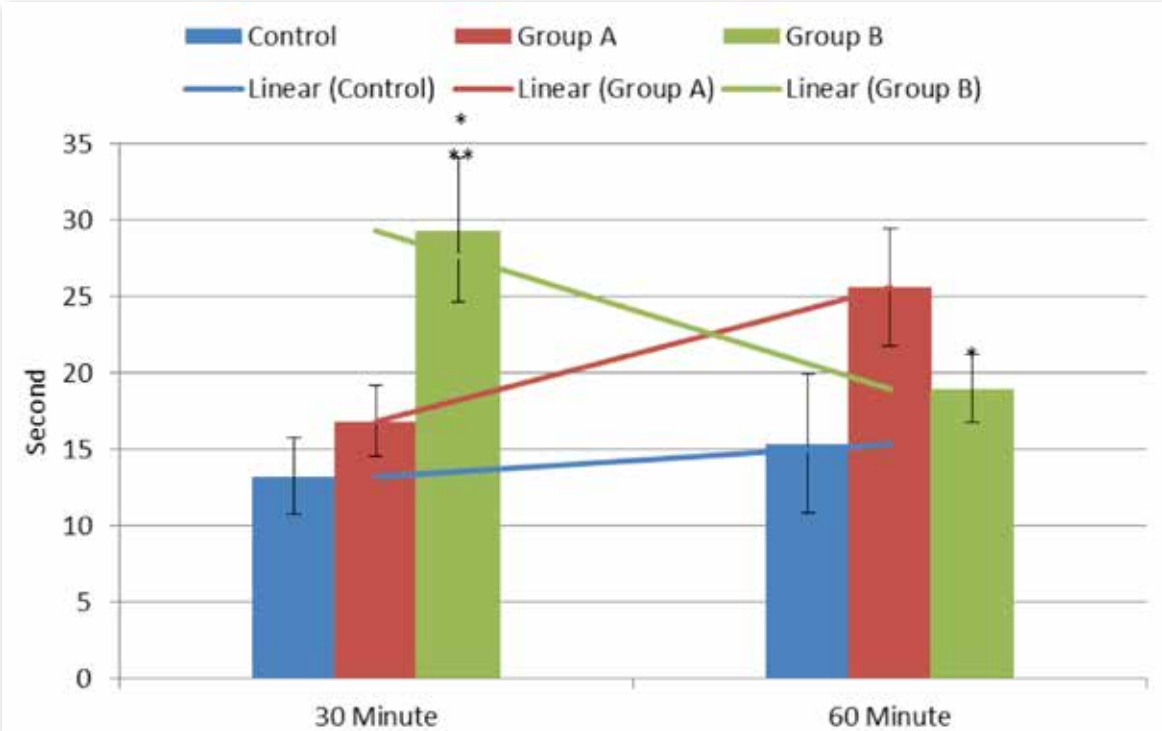

Figure 1: Reaction time of control and agomelatine groups. At the 30th minute groups with the ANOVA statistical analysis is significant differences *P=0.007).
There is a significant difference between Group B and control group over time (**p=0.036) at RM ANOVA with Bonferroni post-hoc test.

doses were chosen having regard to similar studies[26-28].

Because the maximum plasma level was reached in one hour after the oral administration of agomelatine, the hot plate test was performed at the 30th and 60th minutes[29]. Reaction times recorded by using the hot plate method (50^{0}C) were evaluated to reveal nociceptive effects at the 30th and 60th minutes after drug administration. To compare the nociceptive effects of different doses of agomelatine for each time (30th and 60th minute), a one-way ANOVA (analysis of variance) with the Bonferroni post hoc test was used. A repeated measure (RM) ANOVA was used for the evaluation of the groups over the time. The Bonferroni test was also performed as a post-hoc test in the repeated measure ANOVA. The Pearson correlation test was used for the assessment of the relationship between groups. The results were presented as means ± standard error of mean (SEM). The level of statistical significance was fixed at $p<0.05$[30,31].

RESULTS

The hot plate test results were evaluated to reveal nociceptive effects of agomelatine in mice and the pain threshold results are illustrated in Figure 1 and Table 1.

Primarily, the pain threshold values of the agomelatine groups (A and B) were higher than the control group at each time point (30th and 60th minutes). Furthermore, the 30th minute pain threshold findings of group B were higher than those of group A (p=0.007). In the post-hoc Bonferroni test, the groups were compared (Control and A Groups: p=1, C and B groups: p=0.008, A and B groups: p=0.048). At the last time point (60th minute) a contrary situation occurred and the pain threshold values of Group A were found to be higher than those of Group B. However, the difference between groups A and B at the 60th minute were found to be only numerical but not statistically significantly different (p=0.245).

Table 1: Reaction time of control and agomelatine groups

	Control n=8 Mean±SEM	Group A n=8 Mean±SEM	Group B n=8 Mean±SEM	ANOVA	RM-ANOVA
30th minute	13.25±2.48	16.87±2.33	29.37±4.75	p=0.007*	p=0.036**
60th minute	15.37±4.55	25.63±3.87	19.0±2.24	p=0.245	

SEM: Standard error of mean
*=p<0.01, **=p<0.05

Table 2: Test of within subjects effects of RM ANOVA.

	Type III summary of squares	df	Mean Square	F	Significant (P value)
Time	0.333	1	0.333	0.003	0.954
Time and group	754.542	2	377.271	3.918	0.036*

*= p<0.05

Table 3: Test of between subjects effects of RM ANOVA.

	Type III summary of squares	df	Mean Square	F	Significant (P value)
Intercept	19040.333	1	19040.333	184.954	0.000
Group	822.792	2	411.396	3.996	0.034*

*= p<0.05

According to the statistical data, there were no correlations between the Control and agomelatine groups (between Control and A groups; r=0.197, p=0.356 and between the Control group and group B; r=-0.328, p=0.118).

As regards to the Test of Within-Subject Effect (df=1, F=0.003), there were no statistical difference in terms of time effect on results between the groups (p=0.954) (Table 2), but a significant difference in effect was seen between groups (df=2, F=3.996) (p=0.034) (Table 3). In the post-hoc Bonferroni test, significant differences were found between the Control group and group B (p=0.036).

DISCUSSION

In general, depression can be associated with many chronic painful situations[32-34]. It is known that some antidepressant drugs also have an antinociceptive effect; therefore they can be used for the treatment of painful conditions especially accompanied by depression[20,33,35].

Agomelatine is an analogue of melatonin (MT), which is an agonist of MT_1 and MT_2[16,36]. The analgesic effect of melatonin occurs via MT_2 receptors in the nociceptive system[37,39]. It is known that agomelatine has selective agonistic effects on MT_1 and MT_2[17]. In our study, we found that the agomelatine raised the pain threshold in groups A and B (Figure 1). We thought that this might be due to agomelatine's effect on MT_2 receptors. In their study, Yu et al.[38] injected melatonin in rats via the i.p. route and they observed a dose dependent antinociceptive effect. In another study, El-Shenwy et al.[40] found that melatonin had a dose dependent effect increasing the pain threshold in rats. Similarly, we found a dose-dependent effect at the 30th minute, as anticipated. On the contrary, there was no dose dependent analgesic effect in both groups of agomelatine at the 60th minute. This may have been due to an insufficient number of mice in the groups. It is known that 5-HT_{2B} and 5-HT_{2C} receptors also have a role in pain sensing. Like mianserin, mirtazapine and amitriptyline, some antidepressants also have an antagonistic effect on these receptors. Therefore, these antidepressants show analgesic effects on the nociceptive system[17,41,42]. In the literature agomelatine has an antagonistic effect as an antidepressant on 5-HT_{2B} and 5-HT_{2C}[17]. This

information may explain the reason for the increase in the pain threshold in the agomelatine groups. In summary, it can be said that the analgesic effect of agomelatine is due to its agonistic effect on MT_2 along with antagonistic effects on 5-HT_{2B} and 5-HT_{2C} receptors.

Our study has some limitations. Firstly, it would be better if this study had been performed with more different agomelatine doses. Secondly, the groups should have been larger for a further assessment of agomelatine's effects. However, we couldn't find any studies on the analgesic effects of agomelatine in the literature for assessment of agomelatine doses with a ideal number of mice in the groups.

In conclusion, we have not encountered any studies on analgesic effects of agomelatine in the literature, so we thought that this study could be important to shed light on the direction for future studies. To evaluate the effective doses and to clarify the mechanism of the analgesic effect of agomelatine, more studies that are comprehensive should be done. Even this study can contribute to an exploration of the relationship between psychiatric disorders and pain. In addition, agomelatine may be a choice of treatment for patients who have painful conditions with or without psychiatric symptoms.

Conflict of Interest Statement

None of the authors have any financial or other conflict of interest in regard to the present work. This study was performed without any financial or other contractual agreements that may cause conflict of interest.

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