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Effect of agomelatine on ischemic damage in experimental head trauma model in rats

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ABSTRACT

Objective: This study aims to investigate the effect of agomelatine on ischemic injury in an experimentally created head trauma model in rats.

Materials and Methods: Groups: 1) control (C) incisions were made to the coronal and lambdoid sutures and a steel disc was placed without creating a controlled impact acceleration model; 2) head trauma (HT) did not receive any treatment after head trauma with a controlled impact acceleration model; 3) agomelatine (A) 20 mg/kg oral agomelatine given for 7 days after incisions were made to the coronal and lambdoid sutures and a steel disc was placed without creating a controlled impact acceleration model; 4) head trauma+agomelatine (HT-A) 20 mg/kg oral agomelatine given for 7 d after head trauma with a controlled impact acceleration model. The rats were humanely euthanized after the study by ethical protocols, and blood and tissue samples were taken. Biochemical (tumor necrosis factor [TNF]-α and interleukin [IL]-6) and histopathological analyses (terminal deoxynucleotidyl transferase dUTP nick end labeling [TUNEL]) were conducted from these samples.

Results: A significant difference was found in TNF-α between the HT and HT-A groups ($p<0.05$). There was a statistically significant increase in IL-6 in the HT group compared to that in the HT-A group ($p<0.01$). In the histopathological analyses, a decrease in TUNEL-positive cells was observed in the HT-A group compared to that in the HT group

Conclusion: As a result, a decrease in both apoptotic cells and inflammatory responses was observed in the HT-A group. Therefore, more studies should be included.

Keywords: *Agomelatine, Head Trauma, IL-6, Rat, TNF-α*

INTRODUCTION

Head trauma is the most common type that is immediately admitted to the hospital and is related to long-term morbidity and mortality. Head trauma is most frequently caused by car crashes, falls, gunshot wounds, blunt object attacks, sports injuries, and leisure activities (Hardman and Manoukian, 2002). These types of injuries are most common in people between the ages of 15 and 24 and are more common in males. Conditions that increase the harmful effects of trauma include alcohol, previous head trauma, and a history of meningitis, epilepsy, mental retardation, and psychiatric disorders (Adams et al., 1980; Hardman and Manoukian, 2002).

A blow to the head can cause fractures or cracking of the calvaria bones. These fractures can be linear, star, segmental, or collapse, and the intracranial soft tissues receive the impact force. Within milliseconds following the impact, the brain tissue

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is subject to deformation, tears, and crushing. During this severe trauma, the surface of the brain strikes the irregular bony interior of the skull. The areas of the brain damaged by head trauma are usually both adjacent (impact) and opposite (opposite), and the impact results in immediate damage to the neuronal cell bodies, intracranial vasculature, axons, and glial tissue (Kinnunen et al., 2010; Sundman et al., 2015). It is believed that the shock impulse generated by the impact depolarizes the cells through membrane mechanoreceptors. A severe concussion can cause a temporary coma due to impact-induced neuronal depolarization that can spread throughout the cortex. An increase in intracellular calcium concentration, initiated by mechanical depolarization, occurs in the axons, causing cessation of axoplasmic flow and resulting in the death of the distal axon within hours to days (Bayir et al., 2003; MacKay, 2004).

Head trauma is also characterized by other injuries, such as cerebral hypotension, hypoxia, ischemia, excitotoxicity, physiological hormone disruption, and inflammation (Chesnut et al., 1993; Schmidt et al., 2005; Wagner et al., 2012; Kumar et al., 2015). The molecular mechanisms associated with post-traumatic injury cascades are not fully known; however, the activation of neuroinflammation resulting from traumatic brain injury is triggered by the central nervous system (CNS) and peripheral inflammatory responses (Schmidt et al., 2005). These inflammatory responses include proinflammatory cytokines, chemokines, and cell-adhesion molecules (Feuerstein et al., 1998; Ghirnikar et al., 1998; Kumar et al., 2015).

In addition, cytokines exert a neuroprotective effect by reducing angiogenic, neurotrophic, and CNS damage (Morganti-Kossmann et al., 2010; Jeong et al., 2013). Although controlled by physiological mechanisms, chronic post-traumatic disorders and an increase in inflammation may cause blood-brain barrier and neuronal cell dysfunction or death (Shlosberg et al., 2010; Kumar et al., 2015). In addition, previous studies have reported that inflammation and depression are related results (Raison et al., 2006; Dantzer et al., 2011; Haroon et al., 2012). In particular, it is known that depression accompanies both immune suppression and immune activation (Irwin and Miller, 2007). The literature also reports that after depression the concentration of interleukin (IL)-6 and tumor necrosis factor (TNF)-α and proinflammatory cytokines increase in blood and cerebrospinal fluid (Molteni et al., 2013).

A melatonin receptor agonist, agomelatine is a new antidepressant with anti-inflammatory, antioxidant, and antiapoptotic properties (Molteni et al., 2013). A study reported that it may be a new drug candidate against acute neuronal damage secondary to septic disease, as it appears to have antioxidative (Nesterowicz et al., 2023) and anti-inflammatory (Yang et al., 2022) effects through deactivation of NF-kB and increasing SIRT-1 levels (Savran et al., 2020).

A synthetic melatonin analog called agomelatine has drawn interest due to possible neuroprotective benefits, especially when ischemia damage is present. Its antioxidant qualities and function as an agonist of melatonin receptors (MT1 and MT2) are the main explanations for its modes of action. Agomelatine has been shown to reduce ischemia-reperfusion injury, which is important in myocardial infarction and stroke (Hong et al., 2021; Yao et al., 2019; Chumboatong et al., 2017).

This study investigates the effect of agomelatine (N-[2-(7-methoxynaphthalen-1-yl) ethyl] acetamide), whose formula is $C_{15}H_{17}NO_2$, known as an anti-depressant, on inflammation and apoptosis in experimentally induced head trauma. Our working hypothesis is to answer the question of whether agomelatine can be an alternative treatment agent for head trauma.

MATERIALS and METHODS

Four-month-old male Sprague Dawley rats (n=24) weighing between 200-250 grams apiece were used in the investigation. Rats were obtained from Kafkas University Experimental Animals Application and Research Center. Four groups of six rats each were used to categorize the rats:

1. Control (C) incisions were made to the coronal and lambdoid sutures and a steel disc was placed without creating a controlled-impact acceleration model.
2. Head trauma (HT) did not receive any treatment after head trauma with a controlled-impact acceleration model (Albert-Weissenberger and Sirén 2010).
3. Agomelatine (A) given 20 mg/kg oral agomelatine (Les Laboratoires Servier, France) for 7 day after incisions on coronal and lambdoid sutures and steel disc placement without creating a controlled-impact acceleration model (Albert-Weissenberger and Sirén 2010).

4. Head trauma + agomelatine (HT-A) given 20 mg/kg oral agomelatine for 7 day after head trauma with a controlled–impact acceleration model (Albert-Weissenberger and Sirén 2010).

Before the procedure, all rats were anesthetized using intramuscular (i.m.) delivery of 75 mg/kg ketamine hydrochloride (Pfizer, Istanbul, Türkiye) and 15 mg/kg xylazine (BioVeta, Ankara, Türkiye). After anesthesia, the rats were placed on a flat surface in the prone position and a skin incision was made in the coronal and lambdoid sutures. A 10-mm-diameter and 3-mm-thick steel disc was placed on the skull to prevent compression fractures. A head injury model was then created with a free fall of 300 g mass from a height of 1 m. The incisions were primarily sutured.

At the final step of the study (7 days), the rats were euthanized under anesthesia with 75 mg/kg ketamine hydrochloride and 15 mg/kg xylazine IM by the conditions. Samples of tissue (Brain) and blood (intracardiac) were obtained from the rats. The serum from the blood samples was kept at -20 °C until the analyses were completed after they were centrifuged for five minutes at 3000 rpm. The tissue samples taken for histopathological analyses were stored in a 10% formaldehyde solution.

Biochemical analysis

The Enzyme-Linked ImmunoSorbent Assay (ELISA-Elabscience®, Houston, TX, USA) manufacturer's methods were utilized to ascertain the amounts of serum TNF-α and IL-6.

Histopathological analysis

For the histopathological examination of brain tissue in all groups, the tissue was stained after being kept in 10% formaldehyde for 72 h. The samples were dehydrated by putting them through a series of escalating alcohol concentrations after being cleaned in running water for four hours. They were then made transparent by passing then through xylene, infiltrated by passing then through a series of paraffin, and embedded into paraffin blocks (5μm). The tissues were stained using hematoxylin-eosin (H&E) and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL).

TUNEL staining

The TUNEL apoptosis test kit (HRP-DAP) (Elabscience; Cat no: E-CK-A331) was utilized in accordance with the manufacturer's instructions to identify cellular apoptosis in the brain tissues from all groups. From each slide, five fields were chosen at random, and the number of TUNEL-positive cells in each field was counted semiquantitatively. TUNEL staining was characterized by dark staining of apoptotic cells. The ratio of apoptotic cells was evaluated by dividing the number of apoptotic cells by the number of all cells in that area by selecting a 10x10 mm^2 area using the Image J program (Wu et al., 2020).

An Olympus BX43 (Evident Corporation Tokyo, Japan) microscope was used to analyze the TUNEL-positive cells, and an Olympus DP21 (Evident Corporation Tokyo, Japan) camera was used to take pictures of them.

Statistical analysis

Before the study, a power analysis was performed using G-Power 3.1.9.7 (Heinrich Heine University Düsseldorf, Germany). Based on the analyses, the sample size (at least six samples) was decided according to the test power of 0.96 and the significance level of 0.05. A one-way analysis of variance was conducted on all Histopathological parameters to test whether there was a difference among the four groups. Tukey's test was used for mean discrimination among the groups. Hence, $p<0.05$ was used to classify them as statistically significant. The software GraphPad 8.1 (GraphPad Software San Diego, CA, USA) was used for all biochemical analyses. Using SPSS version 22 (IBM Corp. Armonk, NY, USA), Tukey's test of one-way analysis of variance was used to count the TUNEL-positive cells in each group.

Ethical approval

The present study received permission from Kafkas University Animal Experimental Animal Ethics Committee (2020/72).

RESULTS

Biochemical analysis results

In the biochemical analyses, TNF-α and IL-6 parameters were measured to determine inflammation. Within this context, a statistically significant increase in TNF-α was observed in the HT group when the C ($p<0.001$), A ($p<0.0001$), and HT-A ($p<0.05$) groups were compared with the HT group. Additionally, a significant difference ($p<0.05$) was seen between the A and HT-A groups. Between the C and A groups, there was no discernible difference ($p>0.05$) (Figure 1).

A significant increase in IL-6 was seen in the HT group compared to that in the C ($p<0.05$), A ($p<0.01$), and HT-A groups ($p<0.01$). Between the C,

A, and HT-A groups, there was no statistical difference (p>0.05) (Figure 1).

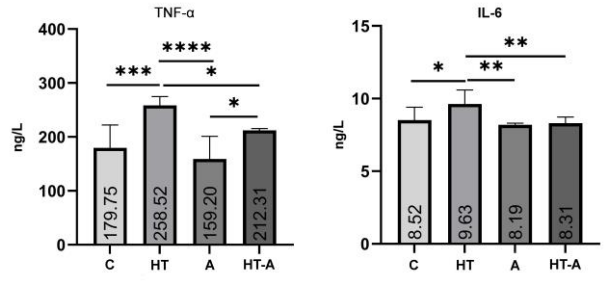

Figure 1. Means and Standard Deviation for biochemical parameters among the four groups. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

Histopathological analysis results

In the H&E staining, local lesioned areas were seen both in the HT group and in the HT-A group. No lesion areas were observed in C and A groups (Figure 2).

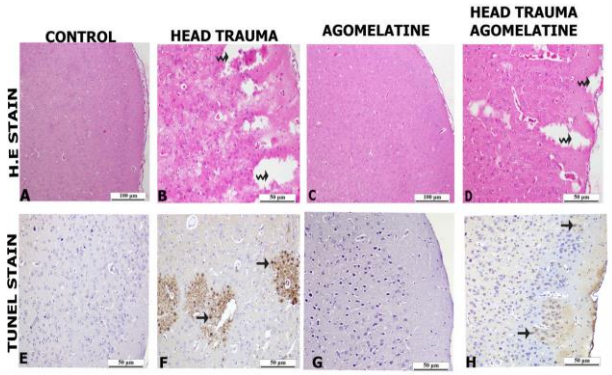

Figure 2. A) Control group hematoxylin and eosin (H&E) staining, 10x. B) Head trauma (HT) group normal arrow: brain defect, 20x. C) A without damage, 10x. D) Head trauma and given agomelatine (HT-A) normal arrow: brain defects, 20x. E) Control group terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining, 20x. F) HT curved arrow: TUNEL-positive cells, 20x. G) A without damage, 20x. H) HT-A curved arrow: TUNEL-positive cells, 20x.

Tunnel staining to determine apoptosis showed that apoptotic cells increased in both HT and HT-A groups. However, these cells increased more in HT group than HT-A group. There was no statistical difference between the C and A groups, according to the statistical results (p>0.05). When comparing the HT group to the C, A and HT-A groups, there was a significant difference (p<0.05). There was statistical difference between the C and HT-A groups, according to the statistical results (p<0.05). Additionally, a significant difference (p<0.05) was seen between the HT and HT-A groups (Figure 3).

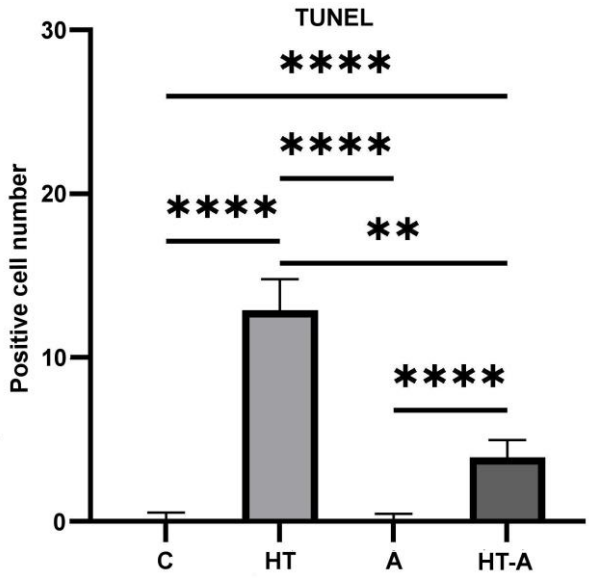

Figure 3. Means and Standard Deviation for the number of positive cells in tunnel staining among the four groups. **p<0.01, ****p<0.0001

DISCUSSION

In both developed and developing nations, head trauma is the leading cause of morbidity and mortality for individuals under 40 years of age. 10% is thought to be the death rate for moderate trauma and 50% for severe trauma. Worldwide, the prevalence of head trauma is reported to be approximately 13/100,000 (Roozenbeek et al., 2013; Mirzaei et al., 2016; Salehpour et al., 2018; Sabouri et al., 2020).

There are two stages of post-traumatic injury. In the first stage, injury occurs in the brain, which causes cerebral microhemorrhage resulting from mechanical damage (Byrnes et al., 2012; Roozenbeek et al., 2013). A decline in cerebral blood flow and oxygenation, harm to the brain's vascular architecture and autoregulation, cytoskeletal disorder, edema, ischemia reperfusion injury, oxidative cell damage, metabolic dysfunction, and ionic hemostasis problem all occur in the second stage (Bramlett and Dietrich, 2002; Sabouri et al., 2020). These conditions cause inflammation and activation of endothelial cells. Additionally, they cause inflammatory cytokines and adhesion factors to rise. The ensuing inflammation speeds up neurodegeneration and neuroinflammation, stimulates glial cells and leukocytes, and causes the production of inflammatory mediators (Davalos et al., 2005; Mirzaei et al., 2016; Salehpour et al., 2018).

Pro- and anti-inflammatory cytokines and chemokines are activated in head trauma. After

head trauma, there is a significant increase in IL-6, IL-1β, and TNF-α astrocytosis and neuroinflammation. The resulting increase occurs approximately 1 h after neurotrauma and increases for up to three weeks after trauma (Liu et al., 2013; Tompkins et al., 2013).

Astrocytosis is the process by which astrocytes, the main glial cells in the central nervous system, become activated in reaction to inflammation or damage. Pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α are frequently released in conjunction with this activation, which can worsen neuroinflammation and cause neuronal injury (Fei et al., 2021; Hu et al., 2021). Fei et al. (2021), for example, noted that enhanced release of these cytokines after neuroinflammation after intracerebral hemorrhage exacerbates early brain injury. Similarly, Hu et al. (2021) observed that increased levels of IL-1β, IL-6, and TNF-α contribute to the inflammatory response, and that traumatic brain injury intensifies neuroinflammation. Like our study, an increase in IL-6 and TNF-α levels was observed in the HT group.

Studies have found that depression increases the level of cytokines (Gałecki et al., 2018) and that inflammation plays a very important role in the pathophysiology of major depression (Maes, 1995; Maes et al., 2011; Leonard, 2014). It is also known that there is a relationship between the serum levels of proinflammatory cytokines IL-1 and IL-6, interferon-gamma, and TNF-α and symptoms of depression. In addition, it has been reported that the administration of antidepressants to patients increases the concentration of anti-inflammatory cytokines such as interleukin-10, while the negative effects of pro-inflammatory cytokines decrease (Colin et al., 2003).

Agomelatine was synthesized during the studies to develop more effective and safer antidepressant drugs in the mid-2000s. It is a synthetic analog of the hormone melatonin, which is synthesized in and released from the pineal gland (Uzbay, 2011). Agomelatine is an agonist of melatonergic MT1 and MT2 receptors as well as an antagonist of the 5-HT2C receptor (Popoli, 2009). Melatonin is a hormone with many regulatory functions that have important effects on the central nervous system. It has remarkable properties as an anti-inflammatory, antioxidant, and anti-apoptotic agent (Yahyavi-Firouz-Abadi et al., 2007). Studies have shown that melatonin regulates its anti-inflammatory effects on both pro- and anti-inflammatory cytokines in various diseases (Park et al., 2007; Mauriz et al., 2013; Habtemariam et al., 2016; Favero et al., 2017; Yu et al., 2017). Carrillo-Vico et al. (2003) have reported that the presence of melatonin receptors regulates the anti-inflammatory pathway by inhibiting TNF-α release. Similarly, Mahmood et al. (2010) have demonstrated the anti-inflammatory effect of melatonin at different doses in chronic inflammation that they created experimentally. It is known that chronic inflammation occurs in multiple sclerosis, and in the initial pathogenesis of this disease, a strong inflammatory-demyelinating process develops. Kang et al. (2009) have reported that melatonin supplements given externally during the inflammatory-demyelinating process improve the myelin status of nerve fibers. In the present study, it is thought that agomelatine, a melatonin agonist, exhibited an anti-inflammatory effect and showed an effect like the study of Kang et al. (2009).

Agomelatine inhibits 5-HT2c receptors in the frontal cortex, which causes an indirect increase in dopamine and norepinephrine (Karamustafalıoğlu and Baran, 2012). Dopamine plays a role in controlling apoptosis in cells that are not neurons as well as neurons. Additionally, dopamine concentrations stimulate the synthesis of anti-inflammatory mediators and prevent the overexpression of adhesion molecules, cytokines, and chemokines brought on by inflammation (Beck et al., 2004). In the present study, both cytokines and anti-inflammation were revealed, and the mechanism of apoptosis was revealed histopathologically. This evidence is believed to reveal that agomelatine exerts its effects by increasing dopamine levels.

It is known that norepinephrine together with cortisone has an anti-inflammatory effect by increasing intracellular CAMP, protein kinase A, glucocorticoid receptors, and β-adrenoreceptors (Straub et al., 2002). By increasing norepinephrine, agomelatine also indirectly increases the anti-inflammatory effect. In this study, the anti-inflammatory effect was observed in the HT-A group.

CONCLUSION

A positive effect was obtained in the HT-A rats. This is thought to be because agomelatine is an antagonist of the 5-HT2C receptor and an agonist of the melatonergic MT1 and MT2 receptors. It is believed that agomelatine, a melatonin agonist, exhibits its therapeutic effect against trauma as an

anti-inflammatory. Since it is an antagonist of the 5-HT2C receptor, it is also thought that, by indirectly raising norepinephrine and dopamine in the frontal brain, it may also exercise its benefits through the anti-inflammatory and anti-apoptotic properties of both dopamine and norepinephrine.

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