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ORIGINAL ARTICLE

The Administration of Melatonin Improved Depressive Behavior in Both Maximal Electroshock Seizure-Prone and Non-Seizure Mice After Undergoing Levetiracetam Treatment

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ABSTRACT

Objectives: Comorbid psychiatric disorders, especially depression, pose challenges in epilepsy. Antiepileptic drugs, including levetiracetam, can also have psychiatric adverse effects, necessitating strategies to address mood regulation. The study aims to assess the impact of melatonin administration on depressive behavior in epileptic and non-epileptic mice.

Materials and Methods: Male albino mice were assigned to different treatment groups. Levetiracetam (20 mg/kg ip) was injected for 14 days; melatonin (25 mg/kg ip) was injected for 7 days. Additional groups were included for epileptic mice. Maximal electroshock was used to induce seizures: locomotor activity, immobility time in the forced swimming test (FST), latency, and food consumption were measured in the novelty-suppressed feeding test (NSFT).

Results: There were insignificant differences in locomotor activity between groups. In the FST, levetiracetam administration significantly increased the immobility duration compared to the control group in epileptic and non-epileptic mice ($p<0.05$). The immobility duration in the levetiracetam-melatonin groups of both epileptic and non-epileptic mice significantly decreased compared to the levetiracetam alone group ($p<0.01$). In NSFT, the levetiracetam group exhibited a significantly longer latency ($p<0.01$) and less food intake ($p<0.05$) compared to the control group; these changes were reversed when levetiracetam-melatonin was administered. In epileptic groups, the difference in latency was insignificant, while food consumption increased significantly ($p<0.05$) in the levetiracetam-melatonin group compared to the levetiracetam-alone group. The results observed with melatonin were similar to those of imipramine.

Conclusion: Melatonin was found to reduce depressive behavior in both non-epileptic and epileptic groups. These results suggest that melatonin could be a potential therapeutic agent for countering the depressive effects of levetiracetam.

Keywords: Depression, melatonin, levetiracetam, epileptic seizure, animal behavior

INTRODUCTION

Depressive symptoms in individuals with epilepsy can have a profound impact on their quality of life, cognitive function, and treatment outcomes, necessitating a comprehensive understanding of the underlying mechanisms and potential interventions.[1,2] Antiepileptic drug (AED) therapy, while essential for seizure control, has been associated with an increased risk of psychiatric adverse effects, including depression.[3] Levetiracetam, a widely prescribed AED, has been specifically implicated in the development or exacerbation of depressive symptoms in patients.[4] Consequently, exploring

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strategies to mitigate the negative impact of AED treatment on mood regulation becomes crucial in optimizing the overall well-being of individuals with epilepsy.[5]

Melatonin, a hormone released by the pineal gland, has garnered considerable attention for its potential therapeutic effects beyond its primary role in sleep regulation.[6] Beyond its established circadian rhythm regulatory functions, melatonin has demonstrated neuroprotective, anti-inflammatory, and antioxidant properties, suggesting a broader role in neurological and psychiatric disorders.[7] In the context of epilepsy, studies have indicated melatonin's anticonvulsant properties and its potential to enhance the efficacy of AEDs, including levetiracetam.[8]

Preclinical studies have confirmed that melatonin administration can alleviate depressive-like behaviors in animal models, including those with epilepsy-related comorbidities.[9] Notably, melatonin has been shown to regulate the levels of neurotransmitters such as serotonin and dopamine, which play crucial roles in mood regulation. By targeting these pathways, melatonin may help restore the imbalance associated with depressive symptoms in individuals with epilepsy.[10,11] Furthermore, an investigation demonstrated that sub-chronic melatonin treatment extended the time it took for pilocarpine-induced convulsions to occur in rats.[12] In a separate study, the persistent use of a melatonin receptor agonist was linked to decreased immobility time in Flinders Sensitive Line rats during the forced swimming test (FST) and an antidepressant influence.[13]

This study aims to evaluate the impact of melatonin administration on depressive behavior in mice treated with levetiracetam, considering the presence or absence of seizures. Behavioral paradigms targeting depressive-like symptoms and locomotor activity will be utilized.

MATERIALS AND METHODS

Animals

Male albino mice weighing 27±2 g (6-8 weeks old) were housed under standard conditions, with access to standard mice chow and tap water, and maintained in a 12-hour light-dark cycle. The mice were acclimated to the behavioral laboratory for 48 hours prior to the experiments. All experimental procedures were conducted in accordance with the guidelines set by the National Ethical Committee of Iran (approval number: IR.MUI.RESEARCH.REC.1401.042, dated: 26.04.2022), to minimize animal distress and the number of animals used in the study. To minimize potential interventions on the animals' behavior, the tests were conducted between 8 AM and 2 PM.

Chemicals

Levetiracetam (Amin Daru Isfahan, Iran), melatonin (Nutralab, Canada), and imipramine (Sigma-Aldrich, Germany).

Study design

The animals were divided randomly into 13 groups, each consisting of 6. A group of mice received levetiracetam (20 mg/kg).[14] The control group received normal saline for 2 weeks. A group received melatonin (25 mg/kg);[15] the control group received the melatonin vehicle (2% ethanol, dissolved in normal saline) for 7 days. A group received levetiracetam for 14 days and melatonin from days 7 to 14. A group received levetiracetam for 14 days and imipramine (10 mg/kg) from days 7 to 14.

There were additional groups for the epileptic mice. The normal group did not receive an electric shock. The study included groups that received levetiracetam (20 mg/kg) or normal saline for 14 days, followed by an electric shock on the 14th day. Groups that received melatonin (25 mg/kg) or imipramine (10 mg/kg) for 7 days were given an electric shock on the 7th day. Two combination therapy groups, the levetiracetam-melatonin and levetiracetam-imipramine groups, were included, which received levetiracetam for 14 days and either melatonin or imipramine from day 7th to 14th, and an electric shock on day 14. All the drugs were injected intraperitoneally; the concentration for all injections was 1mL/100g.

Maximal electroshock (MES)

For the induction of seizures using the MES method, mice were subjected to an electrical stimulus produced by means of an alternating current provided by a Hugo Sachs generator (Rodent Shocker, type 221, Freiburg, Germany). The electrical stimulus (35 mA with a 0.6 second duration) was delivered via ear-clip electrodes connected to the stimulator. The intensity of the electrical current was adjusted to elicit generalized tonic-clonic seizures, characterized by bilateral limb extension and loss of postural control.[16]

Locomotor activity test

This method involved using an open box measuring 40×40×40 cm to evaluate rodents. The animals were placed inside the chamber and allowed to explore for 3 minutes while facing the wall. Total activity was measured by manually recording the vertical activity, while the horizontal movements were recorded by a device that utilized infrared beams to detect the animals' positions.[14]

Forced swimming test (FST)

To conduct this assessment, the mice were placed inside a 2-liter glass container filled with water maintained at 23–25 degrees Celsius and measuring 15 cm in depth. The entire test lasted 6 minutes, with the initial 2 minutes serving as an adaptation period. The subsequent 4 minutes were dedicated to recording the duration of immobility, swimming, and climbing behaviors exhibited by the mice. To prevent hypothermia, the animals were dried in a warm room following the test.[17-19]

Novelty-suppressed feeding test (NSFT)

After a 24-hour period of food deprivation, the animals were placed in a new environment containing food in the center. The test consisted of a measurement: the latency to initiate eating was used as an indicator of feeding motivation and potential depressive-like behaviors. Following the delay period, the amount of food consumed by each animal within the designated 20-minute time frame was measured. This measurement provided insight into the animal's feeding behavior and appetite in response to the novel environment.[20]

Statistical analysis

The mean ± standard error of the mean was used to express the results of all groups. Statistical analysis was performed using one-way analysis of variance followed by Tukey's multiple comparison tests as a post hoc analysis. Results with *p*-values less than 0.05 were considered statistically significant. Data analysis was performed using Excel and GraphPad Prism 9 software.

RESULTS

Effect of MES

The epileptic group was subjected to an electrical stimulus of a predetermined value of 35 mA with a 0.6-second duration, and the tonic bilateral or hind limb extension was taken as the endpoint. Six groups were challenged with electroshocks to ensure that each group yielded at least six mice with seizures. Limb stretching was observed in animals with seizures, and the hind limbs of these animals were outstretched 180° to the plane of the body axis. Animals were housed in a controlled environment for 24 hours, after which the next tests were conducted.

Effect of treatments on FST

In non-epileptic mice, in terms of immobility duration, the group receiving levetiracetam showed a significant increase compared to the control group (NaCl) ($p<0.05$). However, in the groups receiving levetiracetam-melatonin and levetiracetam-imipramine, immobility time significantly decreased compared to the levetiracetam alone group ($p<0.01$) (Table 1, Figure 1A). Regarding swimming duration, the swimming duration in the levetiracetam group was significantly lower than the control group (NaCl) (Table 1, Figure 1B) ($p<0.05$). In the levetiracetam-melatonin and levetiracetam-imipramine groups, swimming durations significantly increased compared to the levetiracetam alone group ($p<0.001$). Results of climbing duration did not yield any significant differences among the experimental groups (Table 1, Figure 1C).

In epileptic mice, the groups receiving levetiracetam or NaCl (control) exhibited a significantly increased average immobility duration compared to the normal group ($p<0.05$), indicating MES-induced depression. The group receiving melatonin showed a significant decrease in immobility duration compared to the control group, suggesting the antidepressant effects of melatonin ($p<0.05$). Similarly, the group receiving imipramine also demonstrated a significant decrease in immobility duration compared to the control group ($p<0.01$). The group receiving levetiracetam-melatonin, similar to the group receiving levetiracetam-imipramine, exhibited significant reductions in immobility duration compared to the levetiracetam alone group ($p<0.01$) and the control group ($p<0.01$) (Table 1, Figure 1E). The group receiving melatonin displayed a significant increase in swimming duration compared to the control group ($p<0.01$), indicating its antidepressant effects, similar to the imipramine group. The group receiving levetiracetam-melatonin and the levetiracetam-imipramine group also exhibited significant increases in swimming duration (Table 1, Figure 1F). No significant differences were observed among the tested groups in terms of climbing duration (Table 1, Figure 1G). There was no significant difference in the locomotor activity when compared to the control group (Table 1).

Effect of treatments on NSFT

In terms of the delay in eating, non-epileptic mice in the levetiracetam group had a significantly longer duration compared to the control group ($p<0.05$). However, the levetiracetam-melatonin group, similar to the levetiracetam-imipramine group, demonstrated a significant decrease in latency compared to the levetiracetam monotherapy group ($p<0.05$) (Table 2, Figure 2A). The amount of food consumed by the levetiracetam group was reduced compared to the control group ($p<0.01$), while melatonin increased food consumption significantly compared to the vehicle EtOH ($p<0.05$) (Table 2, Figure 2B). The levetiracetam-melatonin group, similar to the levetiracetam-imipramine group, demonstrated a significant

Table 1. The results of the total activity count in the locomotor activity test, and the forced swimming test in epileptic and non-epileptic mice

Non-epileptic groups (n=6)		**Control (NaCl)**	**Lev**	**EtOH**	**Mel**	**Lev-Mel**	**Lev-Imi**
Locomotor activity (count)	-	163.3±48.4	214.3±32.9	139.4±48.7	143.6±34.8	153±72.3	127.9±57.3
Immobility time (s)	-	137.4±15.4	181.5±10.1*	123.1±16.2	92.0±16.8	95.9±18.5$^{\#\#}$	86.5±16.8$^{\#\#}$
Swimming time (s)	-	75.8±10.6	39.7±7.6*	68.8±8.6	78.5±7.0	102.1±10.3$^{\#\#\#}$	101.7±6.4$^{\#\#\#}$
Climbing time (s)	-	26.6±14.8	18.7±8.0	48.0±10.5	60.4±16.4	42.0±11.4	50.2±19.2
Epileptic groups (n=6)	**Normal**	**Control (NaCl)**	**Lev**	**Imi**	**Mel**	**Lev-Mel**	**Lev-Imi**
Locomotor activity (count)	155.5±25.6	156.1±21.97	179.0±29.5	119.0±47.57	151±58.3	167±49.2	122.9±54.6
Immobility time (s)	140.8±13.1	179.1±13.3^	178.7±8.3^	105.2±14.2**	122.7±8.3*	110.5±15.8**,$^{\#\#}$	95.8±11.7***,$^{\#\#\#}$
Swimming time (s)	71.3±4.7	47.5±5.1	49.0±5.3	118.7±11.3***	101.0±7.0**	91.2±7.9*,$^{\#}$	114.0±6.9***,$^{\#\#\#}$
Climbing time (s)	17.8±9.0	5.1±2.6	12.3±4.6	16.2±7.7	16.3±3.0	24.8±5.3	30.1±9.4

The data of all groups are expressed as mean ± standard error of the mean. The results were analyzed using one-way analysis of variance with Tukey's supplementary test. The control group received NaCl. The melatonin control group received the vehicle (2% ethanol solution, EtOH). The normal group did not receive maximal electroshock. *$p<0.05$, **$p<0.01$, ***$p<0.001$ vs. control (NaCl) group; $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ vs. levetiracetam-only group; ^$p<0.05$ vs. normal group. Mel: Melatoni, Lev: Levetiracetam, Imi: Imipramine

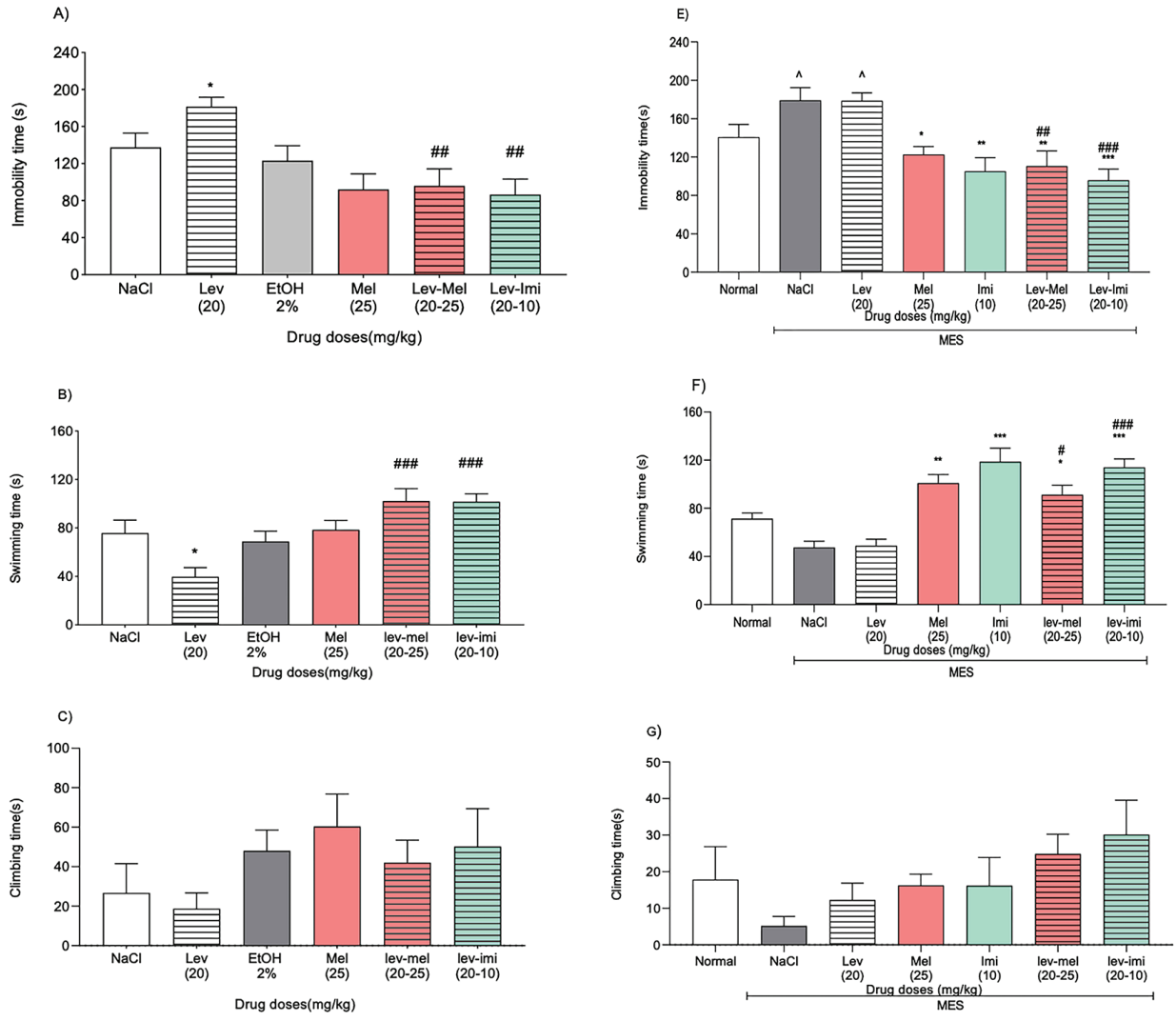

Figure 1. The results of the forced swimming test in epileptic and non-epileptic mice. (A) Immobility duration in non-epileptic mice. (B) Swimming duration in non-epileptic mice. (C) Climb duration in non-epileptic mice. (D) Immobility duration in epileptic mice. (E) Swimming duration in epileptic mice. (F) Climb duration in epileptic mice. Data are expressed as mean ± standard error of the mean. Results were analyzed using one-way analysis of variance with Tukey's post hoc test. The control group received NaCl. The melatonin control group received the vehicle (2% ethanol solution). *p<0.05, **p<0.01, ***p<0.001 vs. control (NaCl) group; #p<0.05, ##p<0.01, ###p<0.001 vs. levetiracetam-only group; ^p<0.05 vs. normal group. Mel: Melatoni, Lev: Levetiracetam, Imi: Imipramine, MES: Maximal electroshock

increase in food consumption compared to the levetiracetam monotherapy group (p<0.05). Based on the findings in epileptic mice, the difference in average duration of eating delay among the experimental groups was insignificant (Table 2, Figure 2C).

Turning to Figure 2D, the average amount of food consumed varied across the different groups. In comparison, the group receiving melatonin exhibited a significant increase (p<0.05) in food consumption compared to the control group, with the average amount indicated in Table 2. The group receiving levetiracetam-melatonin consumed significantly more food (p<0.05 vs. control and levetiracetam alone group), while the difference was insignificant in the levetiracetam-imipramine group. This value in the melatonin and levetiracetam-melatonin groups was significantly higher than the normal group (p<0.05) (Table 2, Figure 2D).

DISCUSSION

According to the results, melatonin co-administration with levetiracetam improved despair behavior during FST and food intake behavior during NSFT in both epileptic and non-epileptic mice. The treatments, including levetiracetam, melatonin, imipramine, and their combinations, did not have a significant impact on the locomotor activity of the mice in this study, regardless of their epileptic or non-epileptic status. Further investigations utilizing additional behavioral tests and depression-related outcome measures would provide an understanding of the effects of these treatments in both epileptic and non-epileptic models.

In this study, it was observed that administration of levetiracetam in non-epileptic mice significantly increased the duration of immobility in the FST, compared to the

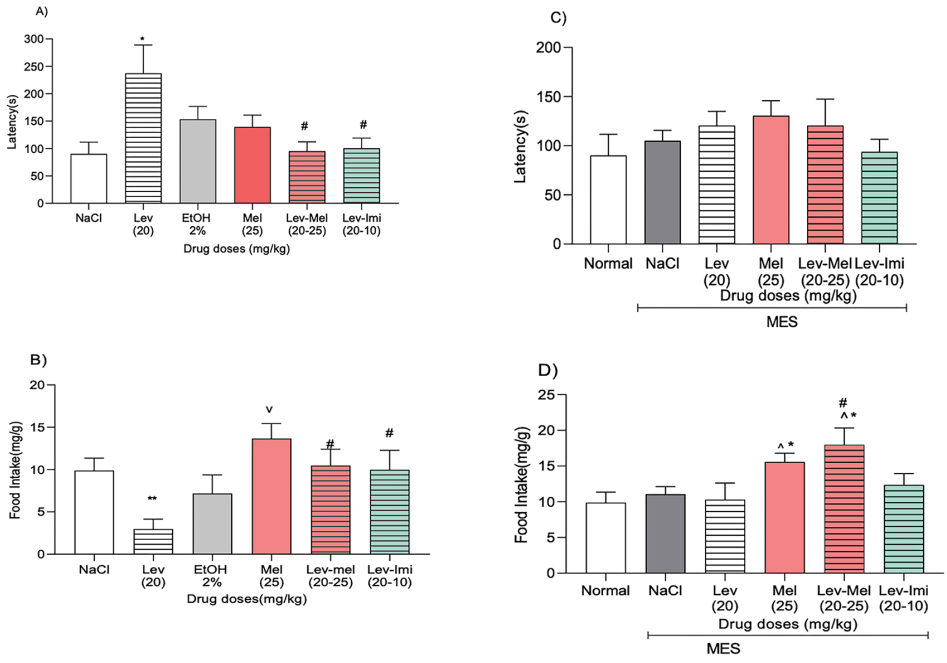

Figure 2. Results of the novelty-suppressed feeding test in epileptic and non-epileptic mice. (A) Latency duration in non-epileptic mice. (B) Food intake in non-epileptic mice. (C) Latency duration in epileptic mice. (D) Food intake in epileptic mice. Data are expressed as mean ± standard error of the mean. Results were analyzed using one-way analysis of variance with Tukey's post hoc test. Control group received NaCl. The melatonin control group received the vehicle (2% ethanol solution). *p<0.05, **p<0.01, ***p<0.001 vs. control (NaCl) group; #p<0.05, ##p<0.01, ###p<0.001 vs. levetiracetam-only group; v sign p<0.05 compared with EtOH group; ^p<0.05 vs. normal group. Mel: Melatoni, Lev: Levetiracetam, Imi: Imipramine, MES: Maximal electroshock

Table 2. The results of the Novelty-suppressed feeding test in epileptic and non-epileptic mice

Non-epileptic groups (n=6)	**Control (NaCl)**	**Lev**	**EtOH**	**Mel**	**Lev-Mel**	**Lev-Imi**
Latency (s)	90.1±21.4	237.3±51.4*	153.3±23.6	139.5±21.2	95.3±16.8###	100.5±18.7###
Food intake (mg/g)	9.8±1.4	2.9±1.1**	7.1±2.2	13.6±1.7v	10.4±1.9#	9.9±2.3#
Epileptic groups (n=6)	**Normal**	**Control (NaCl)**	**Lev**	**Mel**	**Lev-Mel**	**Lev-Imi**
Latency (s)	90.1±21.4	105.0±10.6	120.4±14.5	120.5±27.0	120.5±31.5	93.7±27.0
Food intake (mg/g)	9.8±1.4	11.1±1.0	10.3±2.3	15.5±1.2^'*	18.0±2.3#'^'*	12.4±1.6

The data of all groups are expressed as mean ± standard error of the mean. The results were analyzed using one-way analysis of variance with Tukey's supplementary test. The control group received NaCl. The melatonin control group received the vehicle (2% ethanol solution, EtOH. *p<0.05, **p<0.01, ***p<0.001 vs. control (NaCl) group; #p<0.05, ##p<0.01, ###p<0.001 vs. levetiracetam-only group; ^p<0.05 vs. normal group; v sign p<0.05 compared with EtOH group; ^p<0.05 vs. normal group. Mel: Melatoni, Lev: Levetiracetam, Imi: Imipramine

control group. Additionally, co-administration of melatonin or imipramine with levetiracetam significantly reduced the duration of immobility. These findings suggest that melatonin has antidepressant effects against levetiracetam-induced depression. Previously, it has been demonstrated that the introduction of depression, either by using only levetiracetam or after inducing pentylenetetrazole-triggered seizures in mice by FSTs, led to heightened immobility periods.[21,22]

Previously, melatonin treatment prevented lipopolysaccharide-induced depressive-like behavior in the FST and tail suspension tests, without affecting locomotor activity assessed in the open field test. Melatonin also attenuated the lipopolysaccharide-induced increase in tumor necrosis factor-α levels and the decrease in BDNF levels in the hippocampus. Moreover, melatonin treatment prevented the increase in lipid peroxidation and the decrease in hippocampal glutathione levels.[23] In the current study, a similar pattern was observed in epileptic mice. The group receiving levetiracetam alone exhibited a significant increase in sedentary duration compared to the normal group in FST, but as a similar pattern was observed in the control group, this could be the direct effect of MES. Furthermore, in a separate study investigating the antiepileptic effects of ethosuximide and levetiracetam in WAG/Rij rats with induced epilepsy, ethosuximide was found to improve depression-like behavior; in contrast, levetiracetam exacerbated this symptom.[24]

On the other hand, in the melatonin and imipramine group that received MES, immobility time was significantly lower than the control group. Studies on the effect of melatonin on seizures show that melatonin can reduce seizures.[12,25]

Scientists have noted the anticonvulsant effects of melatonin on penicillin-induced epileptiform behavior in rats. When administered intracerebroventricularly, melatonin extended the delay in epileptiform behavior onset, assessed through electrocorticogram analysis.[26] Experts propose that this observed effect of melatonin might stem from its beneficial influence on GABA-ergic transmission.[12] However, melatonin, like imipramine, also improved despair behavior during the FST in levetiracetam-treated MES epileptic mice, suggesting their antidepressant effect. Therefore, in agreement with both preclinical and clinical research, indicating the advantageous impacts of the melatonin system on anxiety, depression, and epilepsy, melatonin-related substances could offer effectiveness in addressing associated behavioral complexities in epilepsy. This extends beyond simply regulating disrupted sleep-wake patterns.[27] Melatonin and serotonin are primarily involved in regulating sleep and mood. Their synthesis is closely linked, as melatonin is derived from serotonin.[28] On the other hand, daily treatment with melatonin increased serotonin levels, which could be related to its effect on depression, in several brain regions such as the amygdala and midbrain.[29]

The classification of active behaviors during FST into swimming and climbing time would facilitate the differentiation between serotonergic and noradrenergic classes of antidepressant drugs.[30] In epileptic and non-epileptic mice, co-administration of melatonin or imipramine with levetiracetam significantly increased swimming duration, while there was no significant difference in the climbing time. Climbing behavior may not be sensitive enough to detect subtle differences caused by the treatments.[31]

These findings indicate that melatonin can effectively counteract the depressive effects induced by levetiracetam in epileptic mice. Results suggest that both melatonin and imipramine antidepressant effects are possibly mediated through altering the serotonergic system. A related study focused on investigating the antidepressant effects of N-methyl-D-aspartate receptor (NMDAR) blockers following levetiracetam administration in the modified FST showed that levetiracetam significantly decreased swimming time, while the NMDAR blockers increased swimming duration compared to the control group.[14] Therefore, it was supposed that reduced serotonin levels are related to levetiracetam-induced depression. Consistent with these results, a separate study investigating the effects of melatonin and agomelatine on anxiety and depressive-like behaviors induced by doxorubicin in rats observed that pretreatment with melatonin and agomelatine significantly reduced immobility time and increased swimming time in the FST compared to the doxorubicin alone group.[32]

The NSFT is a commonly used experimental approach to assess alterations in eating behavior. By subjecting animals to a novel environment, researchers can examine the impact of unfamiliar surroundings on their food consumption, thereby offering valuable insights into the intricate interaction between environment, stress, and feeding behavior.[33] Notably, despite FST, which is an acute model that evaluates despair behavior, the NSFT detects depressive-like behaviors in mice subjected to chronic treatment, surpassing other assessment methods in this regard.[14] In non-epileptic mice, the latency to eating differed. In the levetiracetam-melatonin group, there was a significant reduction in the eating delay time compared to the levetiracetam group. A similar eating delay was seen with imipramine co-administration. Consistent with these findings, a separate study investigating eating suppression in a novel environment reported that chronic administration of exogenous corticosterone increased the delay time before feeding. This anxiety-related behavior was reversed by chronic administration of melatonin.[34] Significant differences in food consumption were observed in the combined treatment groups of levetiracetam-melatonin and levetiracetam-imipramine compared to the levetiracetam-only group. In epileptic mice, there was no difference in latency time compared with the control group, which implied the dominant effect of MES on the results. The study indicates that melatonin could not reduce the latency time while co-administered with levetiracetam when epilepsy was induced by MES. On the other hand, in epileptic mice, significant differences in food consumption were found among the treatment groups. However, the levetiracetam-melatonin group significantly increased food consumption compared to the groups receiving levetiracetam alone, the control group, and the normal group.

CONCLUSION

Melatonin exhibited beneficial efficacy in alleviating depressive behavior in both epileptic and non-epileptic mice groups. Thus, melatonin holds potential as a therapeutic agent to counteract the depressive effects associated with levetiracetam treatment. Further investigation is warranted to elucidate the underlying mechanisms responsible for melatonin's antidepressant properties. Melatonin, recognized as a naturally produced hormone with potential antiepileptic and antidepressant effects, might hold significant promise in mitigating depression during epilepsy treatment. However, additional investigation through clinical studies is required to further explore this potential.

Ethics

Ethics Committee Approval: All experimental procedures were conducted in accordance with the guidelines set by the National Ethical Committee of Iran (approval number: IR.MUI.RESEARCH.REC.1401.042, dated: 26.04.2022), to minimize animal distress and the number of animals used in the study.

Informed Consent: Not required.

Footnotes

Authorship Contributions

Concept: A.M., Design: A.M., M.R., Data Collection or Processing: A.M., A.Mo., Analysis or Interpretation: A.M., M.R., A,M., Literature Search: A.M., A,Mo., Writing: A.M., M.R., A,Mo.

Conflict of Interest: The authors declare no conflicts of interest.

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