Original Article

J Adv Med Biomed Res. 2024; 32(154): 380-387

# Prophylactic Effect of Melatonin on Action Potential Modulation in Snail Neurons: A Study in a Pentylentetrazol-Induced Epileptic Model

**Marzieh Marahem[1], Mahin Ganjkhani [1]***

1. *Department of Physiology, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran*

**Article Info**

10.30699/jambr.32.154.380

**Received**: 2024/10/03;
**Accepted**: 2024/12/07;
**Published Online:** 31 Dec 2024;

**Corresponding Information:**
**Mahin Ganjkhani,**
Department of Physiology,School of Medicine,Zanjan University of Medical Sciences,Zanjan,Iran
**E-Mail:** mganjkhani@zums.ac.ir

**ABSTRACT**

**Background & Objective:** There is considerable evidence in the field of epilepsy research suggesting that melatonin may have a potential therapeutic role in the treatment of epilepsy. Investigating the effects of melatonin on neuronal electrical activity may provide valuable insight into the development of adjunctive therapies in this context. We aimed to investigate the prophylactic properties of melatonin using the intracellular recording technique in an epilepsy model of snail neurons, which exhibit epileptic behavior similar to that in human neurons.

**Materials & Methods:** To study the impact of melatonin (100 µM) on firing pattern and action potential (AP) configuration in an epileptic condition, the current clamp technique was used on *Helix aspersa* neurons. Recordings were made before and after administering Pentylenetetrazole (PTZ) (25 mM).

**Results:** The findings demonstrated that applying melatonin to cells in normal Ringer's solution did not significantly alter the resting membrane potential (RMP) or the amplitude and duration of the AHP and AP. However, a significant decline in frequency was evident ($P<0.05$). Application of melatonin after PTZ significantly decreased the firing frequency of APs while concurrently enhancing the amplitude of AHP, which had been reduced by PTZ, and hyperpolarizing the RMP.

**Conclusion:** Our study demonstrates that melatonin has protective effects against some of the adverse impacts of PTZ on neuronal firing patterns in *Helix aspersa* neurons. These findings suggest that melatonin may play a crucial role in modulating neuronal excitability, which is important in epilepsy.

**Keywords:** Melatonin, Pentylenetetrazole, Intracellular recording, *Helix aspersa*



## Introduction

Epilepsy is a chronic neurological condition that affects people of all ages, ethnicities, socio-economic statuses, and geographical locations. **(1, 2)**. Despite the high prevalence and long history of this syndrome and the widespread use of antiepileptic drugs, a definitive therapeutic approach for epilepsy remains elusive because current antiepileptic drugs are not effective for all patients and can cause debilitating side effects**(3)**. To gain a deeper insight into the treatment of epilepsy, it is important to directly examine the physiological functions and electrical properties of neurons because the pathophysiology of epilepsy is related to increased abnormal neuronal activity. Intracellular recording of snail neurons provides a unique opportunity to investigate the cellular mechanisms underlying neurological disorders such as epilepsy **(4)**. For instance, convulsants such as pentylenetetrazol (PTZ) have been shown to elicit a potential pattern in snail neurons that resembles the epileptic activity observed in mammalian nerve cells known as paroxysmal depolarization shift (PDS) **(5, 6)**. These electrical events are irregular changes in the voltage of the neuronal membrane. Although transient, PDS lasts significantly longer than the depolarization seen in typical action potentials. PDS typically displays a distinct voltage pattern, beginning with an action potential discharge that gradually diminishes in amplitude until only minor oscillations remain on a depolarized plateau **(7)**. Therefore, it can be used as a suitable model to study cellular effects. Melatonin (MLT), a hormone derived from tryptamine, is an endogenous substance that has an important effect on the nervous system. Melatonin is primarily produced by the pineal gland. It is released mainly during the night **(8)**. This fundamental molecular structure is essential for sustaining life in many organisms, from bacteria to humans **(9)**. Melatonin can potentially enhance brain health and mitigate the risk of serious neurodegenerative and neuropsychiatric dysfunctions

**(10)**. Available clinical and basic science data suggest that melatonin may have therapeutic value in treating epilepsy **(4, 11)** and that it has anticonvulsant properties that are effective against chemically induced seizures **(3, 12)**. The antioxidant properties of melatonin and its low toxicity make it an appealing option for use as an adjunctive therapy in epilepsy treatment **(3).** Based on the current evidence regarding the relationship between melatonin and epilepsy, along with studies suggesting that melatonin may reduce neuronal activity by decreasing excitability in epileptic models and through the inhibitory GABA system **(13)**as well as its inhibitory effects on voltage-dependent calcium channels and reduction of excitatory neurotransmitter release **(14)**, we aimed to study the prophylactic properties of melatonin using the intracellular recording technique in an epilepsy model of snail neurons, which exhibit epileptic behavior comparable to that observed in human cells. The current clamp technique allows for precise measurements of neuronal firing patterns and action potential shapes, which are critical for understanding the electrophysiological changes induced by melatonin**(15).** By measuring parameters such as action potential frequency, amplitude, and resting membrane potential, we can understand how melatonin modulates neuronal excitability under both normal and epileptic conditions.

## Materials and Methods

**Animals**

In this research, the garden snail *Helix aspersa* was utilized, which was collected from the northern region of Iran. The animals were maintained under laboratory conditions and provided with lettuce as a dietary supplement. All experiments were conducted on the F1 neuron, which exhibited sensitivity to PTZ in the subesophageal ganglion. Snail neurons are relatively large and accessible, making them ideal for intracellular recording techniques.

Snails were put in water before the experiment to keep them active. Once the snails had emerged from their shells, the experiments were initiated. First, the shell was removed with a bone cutter. Then, it was attached to the board with a needle. The ganglion mass was dissected and pinned into a recording chamber containing Sylgard 184. The connective tissue was then isolated from the surrounding cells using fine forceps under a stereomicroscope. No digestive enzymes were used in this step. After fixation was completed, certain physical characteristics were utilized to identify the F1 neuron and insert the microelectrode **(6)**. F1 neurons in the right parietal ganglion were visually distinguished by size, color and position relative to other cells**(7)**.

All experiments' phases were conducted per the protocols described in the referenced articles and were also reviewed and approved by Zanjan Medical University's animal ethics committee. (ZUMS.REC.1393.99).

**Solutions and Drugs**

The bathing solution was augmented with melatonin at a concentration of 100 µM (16, 17) and pentylenetetrazol (PTZ) at a concentration of 25 mM. Melatonin was freshly prepared daily and dissolved in a small volume of pure ethanol and saline (0.9% NaCl). It was administered via a perfusion system. The tubes containing the melatonin solution were also wrapped to safeguard against light-induced degradation.

Normal Ringer's solution consists of the following (in mM): NaCl 80, CaCl2 10, MgCl2 5, KCl 4, Glucose 10, HEPES 5, and the pH has been adjusted to 7.7 with Trizma base. All materials were provided by Sigma.

**Intracellular Recording**

The alteration of the action potential was recorded using a microelectrode. Before use the microelectrodes were prepared by drawing borosilicate glass capillaries with internal filaments (Clark Electromedical Instruments, UK) through a puller apparatus (Narishige, Japan). Subsequently, the microelectrodes were filled with a solution of 3M KCl. The silver wire was positioned within the microelectrode glass, coated with Ag/AgCl. The resistance at the tip of the microelectrode ranged from 3 to 5 MΩ (18). This set was associated with the amplifier IX1 (Dagan Corporation). In all experiments, an agar bridge, comprising 4% agar in normal Ringer, was employed as a reference electrode .The apparatus above was maintained within a Faraday cage **(4)**.

Following the insertion of microelectrodes into the neurons, the basic spontaneous neuronal activity was obtained before and following the administration of melatonin and PTZ with an intermittent trend. The data was digitized using an analog-to-digital converter (ADInstrument, Australia) **(6)**. The resulting data were stored for subsequent analysis using LabChart 7 software (ADInstruments, Australia). In these experiments, the electrical activity of the neurons was recorded using the current-clamp technique. A minimum of five cells were recorded and analyzed in each experimental group. Only identified cells with a constant resting membrane potential more negative than -36 mV were included in the data collection. After 5 minutes of primary recording, melatonin (100 µM) was administered to the bath, and recordings were taken for another 5 minutes before PTZ was introduced. In the therapeutic group, PTZ (25 mM) was first added to the Ringer's solution, and after 3 minutes of recording, melatonin was added to the Ringer's solution containing PTZ. It should be mentioned that melatonin's therapeutic and protective effects have been studied in different groups of snails.

Subsequently, the parameters of the action potential were analyzed, including the frequency of spontaneous electrical activity (Hz), duration (mS), and amplitude of the action potential as well as after-hyperpolarization (AHP) amplitude and resting membrane potential (RMP) in millivolts. All AP parameters were measured with the LabChart software.

For further information, the amplitude was defined as the voltage difference from the resting potential to the peak of the first action potential. Duration was measured at 50% of the amplitude of the action potential. Afterhyperpolarization (AHP) was evaluated as the change in membrane potential after the action potential, where the potential becomes more negative than the resting level. The AHP can be quantified by determining its negative peak value relative to the resting membrane potential after the action potential.

**Statistical Analysis**

Data were analyzed using LabChart software. The numerical findings are presented as the mean ± standard error of the mean (SEM). Since the data were parametric, a paired t-test was used to assess the significance of the observed pre-post differences. The statistical analyses were conducted using the SPSS software, and P< 0.05 was considered to indicate statistical significance.

## Results

**Effects of pre-treatment with melatonin on the occurrence of epileptic activity induced by PTZ**

The spontaneous rhythmic firing activity of identified cells (F1 neurons) was initially recorded in normal Ringer's solution, which served as the control group (Figure 1A).

To study the effect of melatonin on the electrophysiological properties of neurons in the absence of any irritant, a solution of melatonin at a concentration of 100 µM was added to the recording chamber. The results demonstrated that melatonin did not significantly influence the resting membrane potential (RMP), action potential amplitude, or AHP amplitude. However, it caused a reduction in action potential frequency ($p \leq 0.01$), indicating a decrease in cell excitability. To address the question of whether melatonin may have anticonvulsant prophylactic effects, PTZ was applied to the bath (Figure 1B). In the presence of melatonin, PTZ did not lead to an increase in firing frequency or a change in RMP. However, it significantly reduced AHP amplitude and increased duration as detailed in Table 1.

**Effect of melatonin on the epileptic activity induced by PTZ**

To gain a deeper insight into the therapeutic or prophylactic effects of melatonin, the impact of this compound was assessed by administering melatonin (100 µM) following the introduction of PTZ (25 mM). Initially, adding PTZ increased spontaneous activity and firing frequency. This was demonstrated by transitioning from regular spiking to burst firing (Figure 1C). Initially, PTZ application significantly increased the frequency of action potentials (APs), accompanied by a decrease in afterhyperpolarisation amplitude and a decrease in resting membrane potential (Table 2). The administration of melatonin after PTZ has been demonstrated to significantly reduce the firing frequency of action potentials in PTZ-induced epileptic conditions ($P \leq 0.001$). Furthermore, melatonin augmented the amplitude of the AHP, which was diminished by PTZ ($P < 0.05$), and also reversed the alteration in resting membrane potential ($P \leq 0.001$). The findings are presented in Table 2.

**Table1. Effect of melatonin on resting membrane potential and some action potential characteristics on neurons before PTZ administration.**

| | Control | Melatonin | MLT+PTZ |
|---|---|---|---|
| RMP(mV) | -40.06 ± 0.50 | -39.53 ± 0.27 | -39.78 ± 0.64 |
| Amplitude (mV) | 44.13 ± 0.97 | 42.43 ± 0.85 | 43.17± 0.88 |
| Duration (ms) | 10.53± 0.21 | 10.58± 0.42 | 14.85± 0.91### |
| AHP amplitude (mV) | -12.25± 0.34 | -11.88± 0.33 | -7.78± 0.55### |
| Frequency (Hz) | 3.19± 0.23 | 2.68± 0.14* | 2.07± 0.05# |

**The data presented represent the mean ± standard error of the mean. (*)Sign indicates significant difference among melatonin and control groups. (* P < 0.05). The symbol # represents a significantly difference between MLT and MLT + PTZ groups (### P ≤ 0.001, # P < 0.05).**

**Table2. Effect of pentylenetetrazol and melatonin (following PTZ) on resting membrane potential and some action potential characteristics, respectively.**

| | Control | PTZ | PTZ+MLT |
|---|---|---|---|
| RMP(mV) | -43.83 ± 0.34 | -38.24±0.45*** | -42± 0.84### |
| Amplitude (mV) | 47.04± 0.95 | 42. 06 ± 0.6*** | 49.00± 1.39### |
| Duration (ms) | 11.32± 0.23 | 12.16±0.27 | 11.32± 0.23# |
| AHP amplitude (mV) | -11.47± 0.31 | -6.46 ± 0.26*** | -7 ± 0.43# |
| Frequency (Hz) | 1.87± 0.07 | 3.08± 0.12*** | 1.52± 0.13### |

**Data presented are mean ± standard error of the mean. The * symbol represents a statistically significant difference between the PTZ and control groups (*** P ≤ 0.001). The symbol # represents a statistically significant difference between PTZ and PTZ+MLT groups (### P ≤ 0.001, # P < 0.05).**

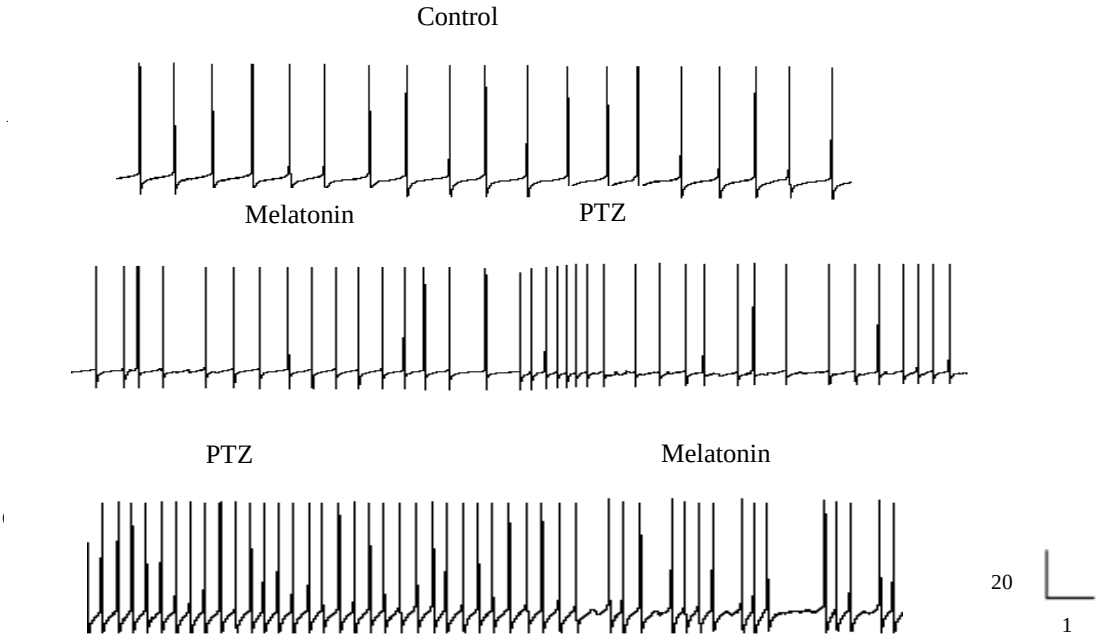


**Figure1. Spontaneous neuronal activity recorded in control group (A). The effect of melatonin on the AP of neurons in normal Ringer's and the effect of PTZ on neuronal electrical activity when pretreated with melatonin (B). The effect of melatonin after PTZ (C).**

## Discussion

Epilepsy is one of the most frequent types of neurological disease **(2).** It is characterized by irregular electrical activity in the brain, where ion channels are critical in regulating neuronal excitability**(19).** Despite the high prevalence and widespread use of anti-epileptic medications, a definitive therapeutic approach for epilepsy remains undiscovered **(3)**. Many patients with epilepsy struggle to achieve long-term seizure control despite the availability of multiple medications. This challenge is due to factors such as seizure variability, drug resistance, delayed drug effects, and patient adherence issues**(20)**. Higher doses of medication, often required for effective treatment, can cause side effects such as dizziness and cognitive difficulties. Further complicating treatment is the need for drugs to cross the blood-brain barrier**(21).** Melatonin has attracted particular interest in this context due to its anticonvulsant effects and positive safety profile**(22)**. To improve patient health and safety, it's crucial to understand the function of melatonin in epilepsy. The antioxidant properties of melatonin and its low toxicity make it an appealing option for use as an adjunctive therapy in epilepsy treatment**(3)**. Melatonin's ability to cross the blood-

brain barrier provides neuroprotective benefits**(23).** Given the existing evidence concerning the relationship between melatonin and epilepsy **(10, 12, 24)**, a considerable number of studies are currently being conducted in this field. Nonetheless, its prophylactic impact on the cellular level has not yet been studied.In the first phase of this study, the administration of melatonin before PTZ prevented the induction of burst activity in response to PTZ. Ayar et al. showed that melatonin can suppress nerve excitability in cultured rat dorsal root ganglion (DRG) neurons by inhibiting high-voltage activated calcium channels (HVA CC) **(25)**. In this regard, it was shown that administration of MLT at pharmacological doses suppressed multiple types of voltage-dependent $Ca^{2+}$ and $Na^{+}$ channels in cultured cerebellar granule cells (CGCs), independent of recognized MLT receptors. Furthermore, characteristics and shape of evoked action potentials (APs) were found to be significantly altered **(26)**. Also, melatonin did not induce a significant change in RMP and prevented depolarization of the RMP after PTZ application. Studies using electrophysiological techniques have shown that melatonin can affect the characteristics of action potentials in neurons**(27)**. Available evidence suggests that melatonin's function in the central nervous system includes influencing neuronal excitability, potentially affecting conditions such as epilepsy**(27)**. By interacting with ion channels and neurotransmitter receptors, it appears that melatonin may alter the resting membrane potential, which is essential for maintaining neuronal excitability and preventing seizures.

In this study, melatonin also did not induce a significant change in AHP in the non-epileptic state, in contrast to PTZ applied in the second phase. Afterhyperpolarization (AHP) is an important electrical event that occurs after action potentials and causes the membrane potential to become more negative than its resting state**(28, 29)**. Calcium-activated potassium (KCa) channels significantly influence this phenomenon, as their activation affects the magnitude and duration of AHP**(29)**. Calcium-activated potassium channels are essential for regulating neuronal excitability and membrane potential**(30)**. They are activated when intracellular calcium levels rise, producing potassium efflux and affecting the AHP that follows action potentials. In various types of neurons, AHP helps regulate firing frequency and prevents excessive neuronal excitability that could lead to excitotoxicity**(31)**. In this study, melatonin did not influence $K_{Ca}$ channels under non-epileptic conditions, and the magnitude of AHP remained unchanged. It is probably because of this point that the influx of $Ca^{2+}$ through the voltage-gated calcium channels, leading to the activation of $K_{Ca}$ currents, didn't happen in the non-epileptic cell.

In the second phase of this study, our experiments demonstrated that the administration of PTZ (25 mM) resulted in alterations to the AP's configuration and firing pattern, leading to an increase in AP frequency. As demonstrated by Klee and colleagues, PTZ has been shown to inhibit spike overshoot and cause frequent firing **(32)**. Based on the available evidence, it can be postulated that the increase in AP frequency results from an increase in positive ion entry or a decrease in potassium current. Under physiological conditions, this would reduce the time between action potentials.

The addition of melatonin (100 µM) following PTZ treatment significantly decreased the firing frequency of APs while increasing the amplitude of AHP, which was decreased by PTZ, and re-increased the reduced resting membrane potential. These results suggest that melatonin may have the ability to alleviate neuronal hyperexcitability. Xu et al. showed that melatonin enhanced large conductance $Ca^{2+}$-activated $K^{+}$ ($BK_{Ca}$) currents but didn't change voltage-gated $K^{+}$ currents and also decreased the size of $Ca^{2+}$ sparks in whole-cell recordings **(33)**. All these can lead to a reduction in hyperexcitability.

## Conclusion

Based on these electrophysiological results, using melatonin before PTZ prevented some of the severe effects of PTZ on the cell. Specifically, prior to PTZ exposure, melatonin administration significantly reduced action potential firing frequency. These findings suggest that melatonin may play a critical role in modulating neuronal excitability and could have therapeutic potential in managing epilepsy. Further research is needed on the preventive effects of melatonin using other electrophysiological assessments such as EEG monitoring. The preventive effect of melatonin on behavioral aspects of different types of epilepsy is also recommended for further research. Regarding the use of melatonin after PTZ, it may have potential inhibitory and antiepileptic effects and could be considered as an adjunctive treatment for epilepsy.

## Acknowledgments

The results described in this paper were part of a student thesis for the MSc degree in Physiology. The authors would like to thank Dr Mahyar Janahmadi for her expert help and advice and the Vice Chancellor for Research Affairs of Zanjan University of Medical Sciences for financial support (grant no. A-12-82-15).

## Authors' Contribution

Marzieh Marahem: Conducted the research project, analyzed the data and prepared the original draft.

Mahin Ganjkhani: Designed the study, supervised the experiments, analyzed the data, revised and edited the manuscript.

## Conflict of Interest

The authors declare that they have no conflict of interest.

## Funding

This research was funded by Vice Chancellor for Research Affairs of Zanjan University of Medical Sciences (grant no. A-12-82-15).

## Ethics Approval and consent to participate

The experimental protocols were approved by the Animal Ethics Committee of Zanjan University of Medical Sciences (ZUMS.REC.1393.99).

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**How to Cite This Article:**

Marzieh Marahem, Mahin Ganjkhani. Prophylactic effect of melatonin on action potential modulation in snail neurons: A study in a pentylentetrazol-induced epileptic model.J Adv Med Biomed Res. 2024; 32(154): 380-387.