Review / *Derleme*

DOI: 10.4274/jtsm.galenos.2024.55477

J Turk Sleep Med 2025;12(1):1-7

Investigating the Relationship Between Circadian Rhythm and Learning-Memory

Sirkadiyen Ritim ile Öğrenme ve Bellek İlişkisinin Araştırılması

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Abstract

The circadian rhythm creates many metabolic changes in our body by influencing the activities of suprachiasmatic nucleus and other centers in the cerebrum according to the light-dark conditions within a 24-hour period. In these mechanisms, melatonin is particularly important in terms of its inhibition in light, and its secretion in the dark. The circadian rhythm, which operates with a negative feedback mechanism, can contribute to various metabolic and genetic functions with oscillations in the cerebrum. Melatonin has a special role in the circadian rhythm; it is controlled by neural, hormonal and genetic factors. The effects of circadian rhythm on learning and memory are determined by observed chemical activities. In particular, there is a strong link between cyclic adenosine monophosphate responsive element binding protein and pre1, and pre2 activation. This link is the most well-known feature of the molecular mechanism of circadian rhythm in memory and learning. As the circadian rhythm is affected by experiences, there may be remarkable changes in molecular mechanisms as well as neuronal activations and genetic mechanisms involved in learning processes and memory formation. Many experimental models on learning and memory have been created so far. The general conclusion is the necessity of the circadian rhythm for learning and memory formation. At the same time, melatonin to provide a healing effect on learning and memory in various dysfunctions.

Keywords: Circadian rhythm, suprachiasmatic nucleus, learning, memory

Öz

Sirkadiyen ritim, 24 saatlik zaman dilimi içerisinde aydınlık-karanlık şartlarına göre serebrumda bulunan suprakiazmatik nukleus ve bezlerin aktiviteleri sonucu vücudumuzda birçok metabolik değişiklikler oluşturmaktadır. Bu mekanizmalarda melatonin hormonunun, ışıkta inhibe olması ve karanlıkta salgılanması açısından ayrı bir önemi vardır. Negatif feedback mekanizmasıyla çalışan sirkadiyen ritim, serebrumda osilasyonlarla çeşitli metabolik ve genetik fonksiyonlara katkıda bulunabilmektedir. Sirkadiyen ritimde özel bir rolü olan melatonin; sinirsel, hormonal ve genetik faktörler tarafından kontrol edilmektedir.

Sirkadiyen ritmin öğrenme ve bellek üzerine etkileri, gözlemlenen kimyasal aktivitelerle tespit edilmiştir. Özellikle siklik adenozin monofosfat duyarlı element bağlayıcı protein ile *Per1* ve *Per2* aktivasyonu arasında güçlü bir bağ vardır. Bu bağ sirkadiyen ritmin bellek ve öğrenme üzerine olan moleküler mekanizmanın en bilinen özelliğidir. Deneyimler sonucu sirkadiyen ritmin etkilenmesiyle moleküler mekanizmaların yanı sıra nöronal aktivasyonlar ile öğrenme süreçleri ve bellek oluşumunda görev alan genetik mekanizmalarda da dikkat çekici değişiklikler olabilmektedir. Şimdiye kadar öğrenme ve bellek üzerine birçok deneysel modellemeler oluşturulmuştur. Bunlardan genel olarak çıkarılan sonuç, öğrenme ve bellek oluşumu için sirkadiyen ritmin gerekliliğidir. Aynı zamanda melatonin hormonu, öğrenme ve bellek üzerinde çeşitli disfonksiyonlarda iyileştirici etki sağlamaktadır.

Anahtar Kelimeler: Sirkadiyen ritim, suprakiazmatik nukleus, öğrenme, bellek

Introduction

Circadian Rhythm

The term "circadian rhythm" refers to the daily oscillations in various biological and physiological processes that are regulated by the transcription-translation of circadian *CLOCK* genes and proteins. Sleep-wake cycles, cognitive functions, and intrinsic clock functions are largely in accordance with circadian rhythm. Disruptions in circadian processes can lead to many pathologies, and therefore, understanding the molecular mechanism of circadian rhythm may help to eliminate many of these pathologies. The molecular mechanism underlying the circadian rhythm is encoded by the twenty-four-hour autoregulatory cycle in the cerebrum, forming a time-determining network in nearly all body tissues.[1] Disorders in the circadian cycle or alterations in genetic activations can result in circadian rhythm disorders. According to the International classification of sleep disorders, third edition, six distinct circadian rhythm disorders have been delineated: delayed sleep phase syndrome, early

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Received/Geliş Tarihi: 20.02.2024 **Accepted/Kabul Tarihi:** 19.03.2024 **Epub:** 03.02.2025 **Publication Date/Yayınlanma Tarihi:** 12.03.2025

Cite this article as: Başer T, Saygın M. Investigating the relationship between circadian rhythm and learning-memory. J Turk Sleep Med. 2025;12(1):1-72025;12(1):1-7

sleep phase syndrome, independent sleep phase syndrome, irregular sleep-wake rhythm, jet lag, and shift work disorder.[2]

Suprachiasmatic Nucleus

The suprachiasmatic nucleus (SCN) is a structure that contains approximately 20,000 neurons, glia, and pacemaker neurons. It is responsible for regulating the circadian rhythm through changes in the day-night cycle, spontaneous firing, and changes in membrane resting potential.[3] Impulses generated by light rays reaching the retinal ganglion cells stimulate the SCN through the retinohypothalamic pathway. The impulse generated by the entry and exit of sodium and potassium ions through the membrane of pacemaker neurons in the SCN reaches the paraventricular nucleus (PVN) and, subsequently, the superior cervical ganglion (SCG) through the intermediolateral column of the medulla spinalis. The post-ganglionic fibers from the SCG extend to the pineal gland, leading to the inhibition of melatonin synthesis.[4] The signals emanating from the SCN stimulate the pineal gland in a dark environment. However, light exposure during the day (it has recently been stated that it is especially blue light) inhibits the pineal gland, decreasing melatonin synthesis and moving away from the appropriate physiological conditions required for circadian rhythm.[5] The SCN is stimulated by the initial light exposure, which subsequently activates cortisol secretion, body temperature regulation, and hormonal mechanisms throughout the diurnal cycle.[6] Stimuli from the SCN then direct the work of peripheral tissues, such as the liver, pancreas, skeletal muscle, and numerous others. It is postulated that each of these tissues possesses an autonomous circadian clock, the regulation of which is facilitated by impulses generated from reactions within the SCN in response to light exposure or absence.[7] It is noteworthy that circadian rhythm exhibits interindividual variability, and SCN activity can be influenced by external signals called zeitgebers, which modulate numerous endogenous and genetic factors. The external signals, termed zeitgebers, play a crucial role in the regulation of circadian rhythm and the perception of the light/dark cycle.[8]

Pacemaker Neurons

These neurons constitute groups that function as the fundamental nodes in the initiation and regulation of circadian rhythm in the SCN of the hypothalamus. Pacemaker neurons have been identified as the site of molecular mechanisms that initiate intrinsic clocks and circadian rhythms.[9] It has been demonstrated that these neurons orchestrate the synchronization of oscillatory movements. Recent studies have demonstrated that the regulation of cellular multiple oscillatory movements is also provided by pacemaker neuron groups. These neurons generate signals that are phase-specific, with each signal contributing to the realization of distinct multi-oscillatory movements across diverse tissues.[10] Lesions or idiopathic dysfunction of these neurons have been demonstrated to induce circadian rhythm disturbances. The SCN astrocytes and neurons have been identified as potential contributors to these disturbances, given their role as distinct branches of the network formed by pacemaker neurons. The SCN, in conjunction with the pituitary gland, the autonomic nervous system, and the brain, plays a pivotal role in regulating the circadian rhythm of oscillatory movements through the reception of light rays.[11]

Melatonin

It is a hormone that is secreted by the pineal gland, which plays a regulatory role in both seasonal and diurnal rhythms, as well as the sleep-wake cycle. The secretion of this hormone is primarily derived from pinealocytes, which are characterized by the presence of lobulated and irregularly shaped nuclei. This phenomenon is attributed to the activation of the SCN in the absence of light. The pinealocytes are accompanied by numerous synaptic bodies, which play a crucial role in axo-dendritic synaptic communications.[12] Melatonin is synthesized from serotonin, and two important enzymes act as catalysts in this synthesis process. These enzymes are N-acetyl transferase (NAT) and hydroxyindole-O-methyltransferase. Norepinephrine, a significant transmitter in the pineal gland, binds to β1 and β1 receptors present on the pinealocyte membrane. It has been observed that 85% of melatonin hormone is secreted in response to stimulation of β1 receptors, while approximately 15% is released following binding to β1 receptors.[13] Upon binding to the designated receptors, norepinephrine elevates the concentration of cyclic adinosine monophosphate (cAMP) and NAT enzyme through the activation of adenylate cyclase in the pinealocyte cell membrane, thereby stimulating melatonin release. The released melatonin is not stored, but rather, it is released directly into the bloodstream.[8] The neural mechanism of melatonin synthesis involves signals originating from the retinohypothalamic pathway, which are transmitted to the hypothalamus. Within the hypothalamus, these signals undergo a series of chemical reactions in the SCN and the PVN. Subsequently, these signals are relayed to the medial forebrain bundle. From there, they pass to the medulla spinalis, where norepinephrine is released from the SCG via post-ganglionic fibers, and enzymatic reactions begin.[14] Numerous models have been developed through the use of chemical induction. In general, after memory and learning dysfunction are induced by using chemicals such as ethanol, thinner, okadaic acid, D-galactose, isoflurane, and its derivatives, experimental studies are performed with melatonin administration. Two salient points emerge from this research. Firstly, the impact of various chemicals when administered concomitantly with melatonin is observed. Secondly, the route of administration plays a pivotal role in the experimental outcomes. It is noteworthy that the outcomes observed through intracerebroventricular (ICV) and intraperitoneal (IP) administration can vary significantly in many experimental models.[15]

Per1 and Per2 Proteins

From a genetic perspective, the *Period proteins1 (Per1)* gene is an important clock factor in the regulation of circadian rhythms. Critical physiological pathways in cellular divisions are subject to the influence of circadian rhythms. The *Per1* gene has been identified as a crucial regulator of these circadian pathways, thereby establishing a link between circadian rhythms and cell division cycles.[16] The *Per2* gene has been identified as a tumor

suppressor gene. Disruption of the circadian rhythm has been shown to lead to the up-regulation and down-regulation of genes that contribute to the development of cancer cells.[4] The *Per1* gene, in particular, has been identified as a critical regulator of the connection between the circadian rhythm and the cell cycle, functioning through the actions of proteins such as brain and muscle ARNT-like protein (BMAL1) and Wee1, which are derived from CLOCK complexes.[7]

Activation of *BMAL1* and *CLOCK* genes leads to transcription of *Per* and *cryptochrome (CRY)* genes in the SCN. The resulting *Per* and *CRY* bind to each other to form a complex. The *Per-CRY* complex inhibits the genes they transcribe, and then this complex degrades, and the twenty-four-hour cycle is completed (Figure 1).

Learning

All the outcomes of education, training, and experiences that lead to long-lasting behavioral changes that are dependent on neural mechanisms are called learning. Many neuronal activations occur with experiences, and the main behavioral changes are due to changes in these neural mechanisms.[17] Perception, understanding, and comprehension are important factors in learning. Therefore, many theories have been put forward about how the complex process of learning takes place. Some of them are behavioral, sensory, cognitive, and neurophysiologically based learning theories.[18] It is a fact that the vast majority of human behaviors are learned behaviors. This dynamic process, involving different types of learning, continues throughout life and is also a determinant of human lifestyle.[19] All formations that emerge as a consequence of learning are considered behaviors. This encompasses a wide spectrum of behaviors, including but not limited to shouting, writing, walking, blushing, and speaking. Subsequent to the acquisition of knowledge, cognitive functions such as thinking, planning, and, most notably, decision-making abilities undergo development. The learning process unfolds through the mechanisms of classical and operant learning. In this process, the nervous system develops a selective adjustment mechanism against special stimuli within intense stimuli.[20] This dynamic process persists throughout the lifespan and is contingent on changes in neural functions. Consequently, learning can be succinctly defined as a phenomenon and/or the process that produces a phenomenon.[21]

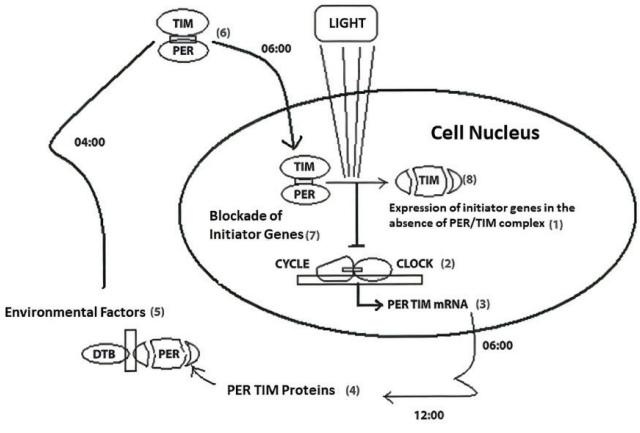

Figure 1. Genetic Mechanism of Circadian Rhythm[2]
TIM: Timeless proteins, PER: Period proteins, DTB: Doubletime proteins, mRNA: messenger-RNA

Memory

Memory can be defined as the cognitive process of storage and retrieval of information. It is not the content of what is read that determines our level of knowledge; rather, it is the retention and subsequent recollection of that information that contributes to our cognitive understanding. The classification of memory is typically based on criteria such as the manner in which information is stored and retrieved, the nature of the information stored, and the duration over which it is retained.[17] Each memory system has a different anatomical organization (Table 1). In different parts of the cerebrum, memory systems exhibit storage activations, which involve dynamic reactions with highly intense neuronal interactions. At the neuronal level, memory mechanisms extend into the cerebrum through chemical channels.[22] When neurons are in close proximity to stimulate each other and one neuron fires repeatedly and persistently, structural and metabolic changes occur in both neurons. Given the substantial number of synapses, it can be posited that memory capacity is potentially infinite. The neocortex, for instance, contains between 1014 and 1017 synapses, suggesting a capacity to retain information over an individual's lifetime. Furthermore, these synapses exhibit a remarkable efficiency in energy utilization. The various categories of memory are associated with distinct functions. These functions encompass the recognition and storage of objects, events, and other information, as well as the facilitation of various physiological processes, including conditioned responses, reflexes, and specific learning mechanisms.[22,23]

Circadian Rhythm and Learning-Memory Relationship

Molecular Mechanism

Many experimental studies so far have shown that circadian rhythm affects learning and memory. Dysfunctions in circadian rhythm exacerbate some neurodegenerative diseases and cause significant regressions in learning and memory mechanisms.[24] Molecular, genetic, and different systemic factors play a role in the relationship between circadian rhythm and memory. In particular, there is a strong link between cAMP-responsive element binding protein (CREB) and *Per1* and *Per2* activation.

Table 1. Classification of memory

Based on retention and retrieval of acquired knowledge	Based on the type of information stored	Based on duration
Declarative memory	Annotated memory	Short term memory
Reflexive memory	Skill memory	Intermediate-term memory
		Long term memory

This link is the most well-known feature of the molecular mechanism of circadian rhythm on memory and learning.[25]

Melatonin, Learning, and Memory

All molecular, genetic, and even epigenetic phenomena related to the circadian rhythm vary according to the day-night cycle, and each peripheral organ has a different clock-zone activation capability. One of these organs is the brain. For comprehensive intellectual thinking, learning, and storage of information in memory, there are ideal night and/or day times. For example, for thinking, learning, and comprehension, the late afternoon hours of the circadian rhythm are ideal, while for short-term memory, the early morning hours are ideal. For long-term memory, the circadian rhythm is ideal later in the day.[26] At every hour of the twenty-four-hour circadian rhythm, interesting vital, intellectual, cognitive, behavioral, and learning reactions take place. The most enigmatic of these is the secretion of the hormone melatonin, which also contributes to learning and memory formation.[27] Melatonin, a hormone secreted exclusively during the nocturnal phase of the day-night cycle, plays a substantial role in the development of memory in the hippocampus. It does so by binding to melatonin receptors (MT1/MT2), which are believed to be present in the hippocampus.[28] Melatonin's regulatory function extends to the circadian rhythm, with its synthesis originating from the amino acid tryptophan. While its memory-related functions are realized by binding to MT1 and MT2 receptors in the hippocampus, it also contributes significantly to learning processes by binding to MT1 and MT2 receptors distributed in the central nervous system (CNS) (especially the thalamus and cerebellum).[6] Following the secretion of melatonin from the pineal gland, the hormone binds to its receptors. This binding activates cAMP, which is formed from ATP through the process of adenylate cyclase activation. In turn, CREB is formed through phosphorylation by protein kinase. This results in a negative feedback loop that affects cAMP-responsive element (CRE). Consequently, the Per1 and Per2 proteins, which are formed by stimuli to CLOCK and BMAL complex through a chain of reactions at the molecular level that restart from CRE, establish a significant link between circadian rhythm and cellular cycle.[8]

Table 2. Experimental models demonstrating the effect of melatonin on learning and memory

Model	Impact on learning and memory
Down syndrome model	In the Morris Water Maze test, a significant improvement in melatonin, spatial learning and memory
Alzheimer's disease model	Slowing the progression of learning and memory dysfunctions
	Activating mechanisms to protect learning, memory, and different mnemonic functions
	Slowing down memory in the process of deterioration
	Reducing spatial and non-spatial cognitive deficits
	Regulating and improving learning, memory, and cognitive functions
	Improvement of working memory on T-maze of rats induced by bacterial lipopolysaccharide
Sleep deprivation model	Reversing the process of cognitive impairment
	Preventing dysfunction of memory formation mechanisms

Ideal Time Frames for Learning and Memory Activation

The hippocampus contains a large number of MT1/MT2 and also has a major role in learning, memory, and different intellectual functions. In addition, the hippocampus, which has multifaceted circadian information integrations, has gene expressions, neurogenesis activities, and epigenetic components that have not yet been explained. Therefore, it is possible to talk about the most active hours of learning and memory in the day/night cycle in the limbic system parts that contain many complex components related to circadian rhythm.[29] As has been previously reported, there are optimal periods during the day and/or night for comprehensive intellectual thinking, learning, and information storage in memory. Specifically, the early morning hours are conducive to short-term memory, later in the day is optimal for long-term memory, and late afternoon is the most favorable circadian time for learning.[26] However, it appears to be physiologically implausible to sustain the same pace of work, learning, and memory activation throughout the day. Personal motivations have been demonstrated to be ineffective when confronted with learning patterns that do not align with the circadian rhythm. The period of greatest learning and memory activation occurs a few hours after the onset of the day, but this level diminishes shortly after noon.[30] A multitude of studies have demonstrated that the optimal temporal windows for enhancing learning and memory within the circadian rhythm are early morning and late afternoon. Apart from these phenomena, which may vary according to physiological functions, there may also be different time periods in which individual efficiency is in question due to molecular and genetic functions in other limbic system components, especially hippocampal reactions.[31] A more thorough examination of the general concept of "learning" reveals its many facets, including behavioral learning, life learning, mathematics, literature, and language learning. For each of these learning modalities, optimal circadian rhythm times and distinct functional areas of the cerebrum are activated. For instance, in the context of language learning and memory, the optimal time for the most efficient recording function varies according to chronotype and is in the morning and evening.[32]

Chronotype and Learning

Chronotype, defined as an individual's preferred timing for activities based on their circadian rhythm, is a behavioral manifestation that underlies circadian rhythm. That is to say, it is a personality trait that affects circadian rhythm preference. Physiological measurements have categorized individuals into three chronotypes: morning people, evening people, and those who do not fit neatly into either category. Individuals identified as evening types typically engage in nocturnal activities later in the evening and experience higher levels of alertness and cognitive function in the afternoon, which corresponds with

the period of peak memory and learning skills. Conversely, morning people tend to retire early and rise early. The time frame in which optimal learning and memory activation occurs may vary according to chronotypes.[33] The initiation of learning is typically influenced by innate, need-based, and personal motivations. In the chronobiological framework, innate, cue-based learning motivations are of particular relevance.[34] It has been demonstrated that there is a relationship between the propensity for chronotypic behaviors in learning and the presence of need-driven and personal motivations. The hypothesis that the activation of *CLOCK* and *BMAL1* genes in the SCN is the catalyst for these behaviors is supported by research findings. Notably, the optimal learning periods are observed across genders. The genetic reaction cycle of *CLOCK* and *BMAL1* genes in the SCN persists for a designated period following the dissipation of daylight in the evening hours, thereby enabling males to engage in learning activities during these nocturnal periods. This phenomenon is referred to as the eveningist chronotype.[35] A more detailed examination of the relationship between chronotype and learning reveals that the pivotal factor is the interplay between sex and genetic configurations. The temporal framework for chronotypic behaviors is delineated by the activation time of the primary genes in the circadian rhythm mechanism and the subsequent reaction timings that persist after light. It is noteworthy that chronotypic behaviors are implicated in a wide array of physiological and psychological mechanisms. From the vantage point of connectivity with components involved in learning mechanisms, the involvement of disparate pathways accentuates the significance of all data that can be obtained in the chronotype-learning relationship.[36] Genetic arrangements and timings in the SCN, where the time frames of all physiological changes are determined, affect behaviors for innate and different personal needs. The genetic arrangements that underpin these behaviors are shaped by the interplay of *CLOCK*, *BMAL1*, *Per*, and *CRY* genes within the SCN, which undergo a series of chain and cyclic reactions.[37]

Studies on Circadian Rhythm, Learning and Memory

The effects of circadian rhythm on learning and memory have been shown in many studies, and any dysfunction related to circadian rhythm significantly reduces learning and memory ability. Some peptides cause this dysfunction; the most well-known of these is the molecule called Aβ31-35. It has been shown that learning and memory processes are favorable with other molecules that act as antagonists to this molecule. Aβ31-35-induced memory and learning dysfunctions may improve with exendin-4 administration.[24] A normal circadian rhythm is essential for learning and memory. Disruptions to the circadian rhythm, whether caused by neurodegenerative diseases, environmental factors, or pathophysiological conditions, have been shown to have a detrimental impact on learning and memory processes. Amyloid β1-42 (Aβ1-42) molecules have demonstrated efficacy in various neurodegenerative conditions, notably Alzheimer's disease. These peptides have the potential to enhance learning and memory processes by mitigating various circadian rhythm-disrupting factors within the CNS. Aβ peptides, which exist in multiple forms, have been shown to reduce oxidative stress and neurotoxicity and have been found to be effective in other dysfunctions that cause circadian rhythm disruption and positively affect learning processes according to chronotype characteristics. Aβ peptides have been shown to facilitate functional recovery by reducing stress and toxicity in specific receptor areas, particularly within the limbic system. It is imperative to note that a healthy circadian rhythm is a prerequisite for optimal learning and memory. Disruptions to the circadian rhythm, whether induced by neurodegenerative diseases, environmental factors, or pathophysiological conditions, have been shown to have a detrimental impact on learning and memory processes. Aβ1-42 molecules have demonstrated efficacy in various neurodegenerative conditions, particularly Alzheimer's disease. These peptides have the potential to enhance learning and memory processes by mitigating various circadian rhythm-disrupting factors within the CNS. Aβ peptides, which exist in multiple forms, have been shown to reduce oxidative stress and neurotoxicity and have been found to be effective in other dysfunctions that cause circadian rhythm disruption and positively affect learning processes according to chronotype characteristics. Aβ peptides have been shown to facilitate functional recovery by reducing stress and toxicity in specific receptor areas, particularly within the limbic system.[38] The hippocampus and amygdala play a fundamental role in learning, memory, and storage of acquired information. Memory activations in these regions are the result of electrical currents mediated by long-term potential spiking (LTP) and long-term potential depression (LTD). Briefly, a different definition of memory is LTP/LTD refers to the strengthening/weakening of synaptic connections between neurons. This dynamic process of synaptic connections is called synaptic plasticity.[39] Increasing the concentration of melatonin, which binds to a large number of MT1/MT2 receptors in the hippocampus, and perhaps the routes of administration (such as ICV and IP) in rats used in the experiments may be effective in regulating memory mechanisms affected by sleep disorders.[40] LTP and LTD activations or substitution or inhibition of different molecular mechanisms may be effective in this regulation. Studies show that the melatonin hormone contributes to memory formation mechanisms and even provides an effective learning, memory, and storage opportunity despite dysfunctions such as various sleep disorders.[41] The enzyme photolyase, which plays a fundamental role in DNA repair, is absent in many species of animals, plants, and microorganisms but can be found in some viruses. The enzyme photolyase has the ability to utilize photons of blue light. This ability enables it to repair pyrimidine dimers on DNA. Humans lack the enzyme photolyase; however, they possess two structurally analogous essential proteins that do not possess any repair functions. These proteins, designated as *CRY*, function as photoreceptors to regulate the circadian rhythm.[42]

The fundamental cascade of the photolyase enzyme in DNA repair can be elucidated as follows, given the presence of proteins that are absent in humans but share some structural similarities: ultraviolet radiation converts two adjacent pyrimidines into

cyclobutane pyrimidine dimer. The adjacent pyrimidines include thymines, and the enzyme photolyase is activated. This enzyme utilizes the energy of blue light to break the abnormal bond that causes this adjacency. Following this process, the enzyme photolyase converts the adjacent thymine dimer into two normal thymines, thus completing the DNA repair process. This repair process also eliminates the potentially harmful effects of DNA when the thymines are adjacent.[43] It is noteworthy that proteins analogous to the enzyme photolyase, a cryptic enzyme absent in placental mammals, have been identified in humans. As previously mentioned, these enzymes are classified as *CRYs.* CRY proteins exhibit two distinct forms, designated as *CRY1* and *CRY2*. These proteins have been demonstrated to function as receptors, contributing to the regulation of the circadian clock. The impact of *CRYs* on learning and memory remains to be fully elucidated.[44] The primary conclusion of the studies demonstrating the effects of melatonin and circadian rhythm on learning and memory with various models is that learning, memory, and different storage functions can be enhanced by affecting LTP/LTD activations, different molecular mechanisms, and genetic and neuronal factors.[45,46] It is important to note that experimental studies are ongoing, and these studies are guided by models that demonstrate the effects of melatonin on learning and memory.[47,48] Experimental models used in the complex processes of circadian rhythm maintenance are the Down syndrome model, sleep deprivation model, and Alzheimer's disease model (Table 2).

Conclusion

The regulation of circadian rhythm is the result of genetic activations and inhibitions in the SCN. The circadian rhythm, initiated by pacemaker neurons, is influenced by genetic factors. While melatonin, secreted from the pineal gland, acts as the primary regulator of this process, different neurophysiological mechanisms also contribute to the circadian rhythm. The genetic regulation of the circadian rhythm is generally understood to occur as follows: *CLOCK* and *BMAL1* genes in the SCN are activated by daylight through the retino-hypothalamic pathway, which then transcribe *Per* and *CRY* genes. The resulting *Per* and *CRY* genes bind to each other, resulting in the inactivation of the transcribed *Per* and *CRY* genes. Subsequently, especially in the absence of light, the Per and *CRY* genes linked to each other degrade, and the inactive *Per* and *CRY* genes become active again. It is very important to examine the phenomenon of learning, which is defined as behavioral changes that occur as a result of changes in neuronal activations, formation of new connectivities and consolidations, together with memory. Because the first stage of learning, short-term memory, and different memory mechanisms are intertwined. The effects of circadian rhythm on neuronal activations and inhibitions that activate learning memory are manifested by chronotypic behaviors. Genetic, molecular, and endocrine systems that enable the realization of circadian rhythm play a role in innate, need-based, and self-motivated learning. Genetic mechanisms constitute the main framework of the twenty-four-hour cycle of the circadian rhythm in chronotype behaviors that enable better learning. The fact that *CLOCK/BMAL1* genes, which are activated by light, still continue light-related reactions for a while in the dark environment may be the cause of chronotypic behaviors in learning. The impact of the circadian rhythm on learning and memory is dependent on molecular, neuronal, and genetic factors. Hormones such as melatonin have been shown to have significant effects on memory and have been found to ameliorate certain dysfunctions. Consistent with the findings, all studies on circadian rhythm demonstrate its definitive impact on memory. Notably, the 2015 Nobel Prize in Chemistry was bestowed upon Professor Dr. Aziz Sancar for his seminal contributions to this field. The restorative effect of the photolyase enzyme on pyrimidines, as discovered in recent studies, holds significant promise for further research on the enzyme's potential impact on learning and memory. Clinical studies have demonstrated that individuals in specific occupational groups are predisposed to shift-lag circadian rhythm disorders. In a study conducted in 2019, the sleep quality of nurses working in a shift system was investigated. The results obtained from this study demonstrate that sleep quality is impaired in individuals belonging to this specific occupational group. A similar study stated that shift work has harmful effects on cognitive health. The impact of sleep quality on learning and memory is unavoidable; therefore, circadian rhythm disturbances should be regarded as the primary factor influencing learning-memory mechanisms.

In the pandemic affecting the whole world, COVID and its variants cause anomalies in the sleep-wake cycle and circadian rhythm disorders as well as special occupational groups. In addition, COVID-19 anxiety and fear significantly reduce sleep quality and quality of life. Comprehensive and different studies are needed better to define the dimensions and types of circadian rhythm disorders.

Footnotes

Authorship Contributions

Concept: T.B., Design: M.S., Data Collection or Processing: T.B., Analysis or Interpretation: T.B., M.S., Literature Search: T.B., Writing: T.B., M.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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