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Chapter

Circadian Modulation of Neurodevelopment in the Adult Human Brain: Importance of Melatonin

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Abstract

Melatonin (*N*-acetyl-5-methoxytryptamine) is an indoleamine synthesized by the pineal gland in the dark phase of the photoperiod. Released melatonin into the pineal recess and the cerebrospinal fluid is the chemical signal that conveys information about the environmental illumination to the brain. In recent years, it was described that melatonin stimulates the neurodevelopment in the adult brain. During this complex process, new neurons are formed and differentiate to form synaptic connections. Neuropsychiatric disorders are characterized by the loss of neuronal connectivity and diminished levels of melatonin, among other features. Importantly, these patients have impaired circadian rhythms. In recent years, evidence aroused indicating that neurodevelopment occurs in the adult brain, making important the study of chemical compounds and endogenous molecules that stimulate neurodevelopment to reestablish synaptic connectivity. In this chapter, we will review the evidence that supports the circadian melatonin modulatory effects on neurodevelopment and its importance for the treatment of neuropsychiatric diseases.

Keywords: circadian rhythms, melatonin, neurodevelopment, dendritogenesis, axogenesis, neuropsychiatric diseases

1. Introduction

The rotation of the Earth on its axis is the root of the 24-h light-dark cycle and all of the astronomical phenomena that are measured concerning the plane of the horizon—the sunrise and sunset, twilight periods, photoperiod, solar eclipses, movement of the tides, and the lunar perigee and apogee. These phenomena all have the common denominator that they cause variations in the periods of light versus darkness. This light-dark cycle and its variations directly influence the myriad of

activities of living organisms, including sleep and wakefulness, rest and activity, feeding, and body temperature changes [1].

The timing and pattern of mammalian behavioral activities are regulated by an evolutionarily optimized interplay between the genetically based biological (circadian) clock and superimposed environmental factors and thus mask the effects mediated by the clock. The main regulator in endogenous circadian rhythms is the suprachiasmatic nucleus, which sits above the optic chiasm and, in humans, is composed of approximately 20,000 neurons. The most important external synchronizing factors, or "Zeitgebers," is the light-induced phase-setting of the circadian rhythmicity to the 24-h solar day. This influence results in a roughly 24-h activity-rest cycle in diurnal organisms and the converse rest-activity cycle in nocturnal organisms.

Although the 24-h light-dark cycle is the most important Zeitgeber, there are many other modulators that further synchronize or mask circadian rhythms, including social stimuli, sounds, smells, or physical contact, which generate behavioral states that impact endogenous clocks [2]. Regarding the light-dark cycle as a Zeitgeber, the production of melatonin (5-methoxitriptamine), an indolamine secreted by the pineal gland, is dependent on the photoperiod. This hormone is released at night by the pineal gland and collected by the internal recess, the third ventricle. From this location, melatonin is distributed by the cerebrospinal fluid to the brain tissue acting as a synchronizing signal of the internal media with the environmental light [3]. The circadian production of melatonin by the pineal gland is controlled by the circadian clock through a multi-synaptic pathway and released melatonin carries the timing information to the peripheral oscillating structures to couple the oscillating functions (**Figure 1**).

The role of melatonin as circadian messenger, as well as the organization of the circadian system, has been described mainly using confined animals; however, studying biological rhythms under natural conditions allows us to understand how geophysical variables impact endogenous clocks. In this regard, initially, chronobiologists conducted their studies under experimental laboratory conditions, while behavioral ecologists have focused their research on observing the behavior of free-living organisms. In the year 2000, in their book "Activity patterns in small mammals" Halle and Stenth of the University of Jena in Germany proposed the integration of behavioral ecology and chronobiology under natural and semi-natural conditions, founding the new discipline of "behavioral chrono ecology," that is, the study of rhythms under natural conditions and the synchronization of rhythms with nature [4].

In behavioral field studies of primates' activity rhythms and their modulation by environmental variables, the possible dual, synchronizing and/or masking effects of variables other than light-dark cycles are often ignored. However, there are some studies that addressed these issues. One of these was studied in the Mexican spider monkeys (*Ateles geoffroyi*) using long-term activity recordings with wearable accelerometer/data-logger devices (**Figure 2**). The relationship between astronomical and meteorological parameters and various parameters of the monkeys' rest-activity rhythm under semi-natural conditions was analyzed. The monkeys were exposed to natural light, temperature, and humidity cycles. By recording the monkeys' activity for 180 days, the monkeys rested during the night and were active throughout the day with two peaks in activity. Activity time, onset and end of activity, and the timing of their two activity peaks were significantly correlated with duration of the solar day and sunrise or sunset time. Beyond the light-dark cycle, weather, temperature, cloudiness, and artificial variables introduced by their interactions with humans also significantly influenced the duration and times of onset and end of activity [5].
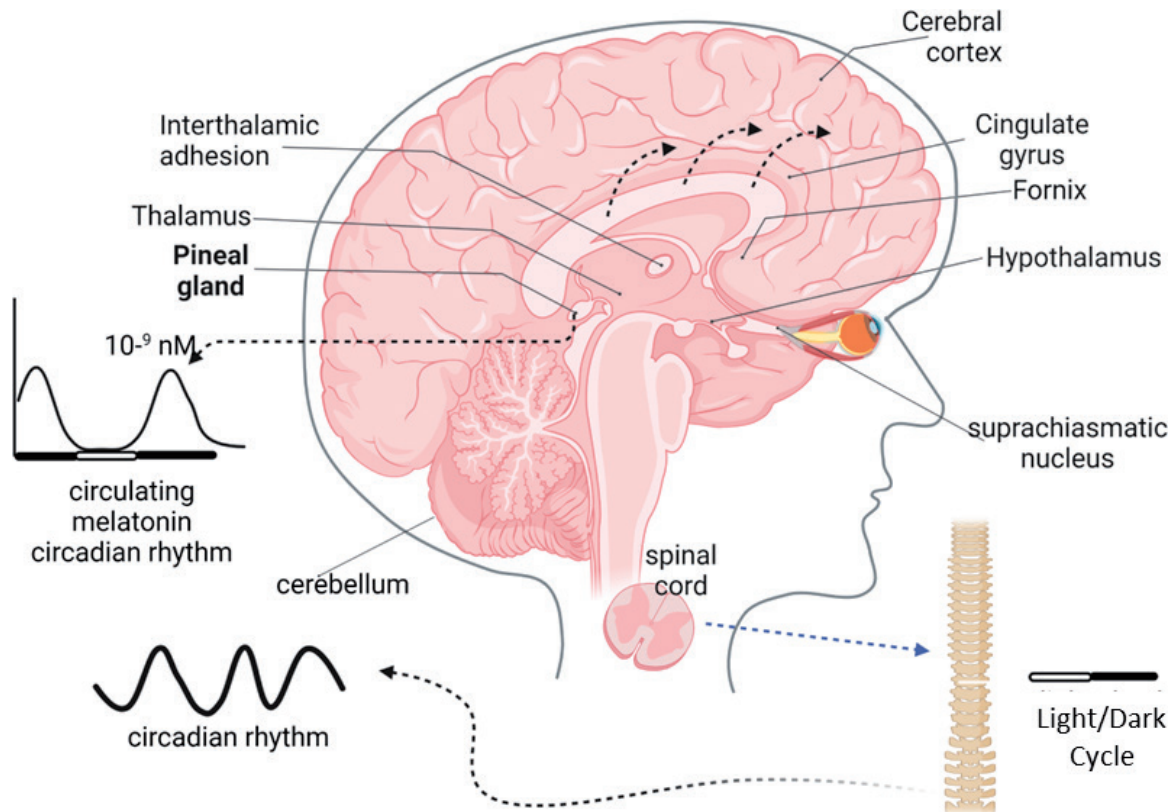
Figure 1.
Regulation pattern of melatonin synthesis. In the scheme is showed the principal structures involved in the circadian rhythm of melatonin synthesis, the suprachiasmatic nucleus and the pineal gland as well as the neuronal and the endocrine pathways to transmit the circadian information, the autonomous nervous system and the variation of circulating melatonin.

In other study, additional environmental variables such as the effect of housing conditions and season were incorporated to the daily timing and pattern of activity in this species. Thus, the activity patterns between monkeys living under natural lighting and climatic conditions in either a large wire netting cage or a 0.25-ha forest enclosure in the primatological field station of Veracruz State University near Catemaco, Mexico, were studied. Also, a pregnant female was followed in the forest enclosure, which gave us insight into the effect of late pregnancy and parturition on the monkey's activity rhythm. Spider moneys are strictly diurnal, with 90% of their total activity occurring during daylight. Monkeys that lived in the forest enclosure had a higher second activity peak in the late afternoon compared to those living in the caged area, resulting in a more pronounced bimodal activity pattern. The spider monkeys kept there had an earlier activity onset and morning activity peak than their conspecifics in the cage; however, no differences were found in the phase-setting parameters of the circadian system to the environmental 24-h periodicity, either by comparison or correlation with the sunrise and sunset. The late pregnancy, parturition, and lactation induced a reduction on the activity level during the week of parturition and the following week. The long days of the summer season and the short days of the winter season were decisive in the expression of the activity time of the morning and evening peaks. Together, data suggest that in Mexican spider monkeys, a weak circadian component and strong direct masking effects of multiple environmental factors are involved in the regulation of the daily activity rhythm [6].

The study of the monkeys under their natural environment may allow us to obtain evidence to highlight the importance of melatonin to modulate diverse oscillating
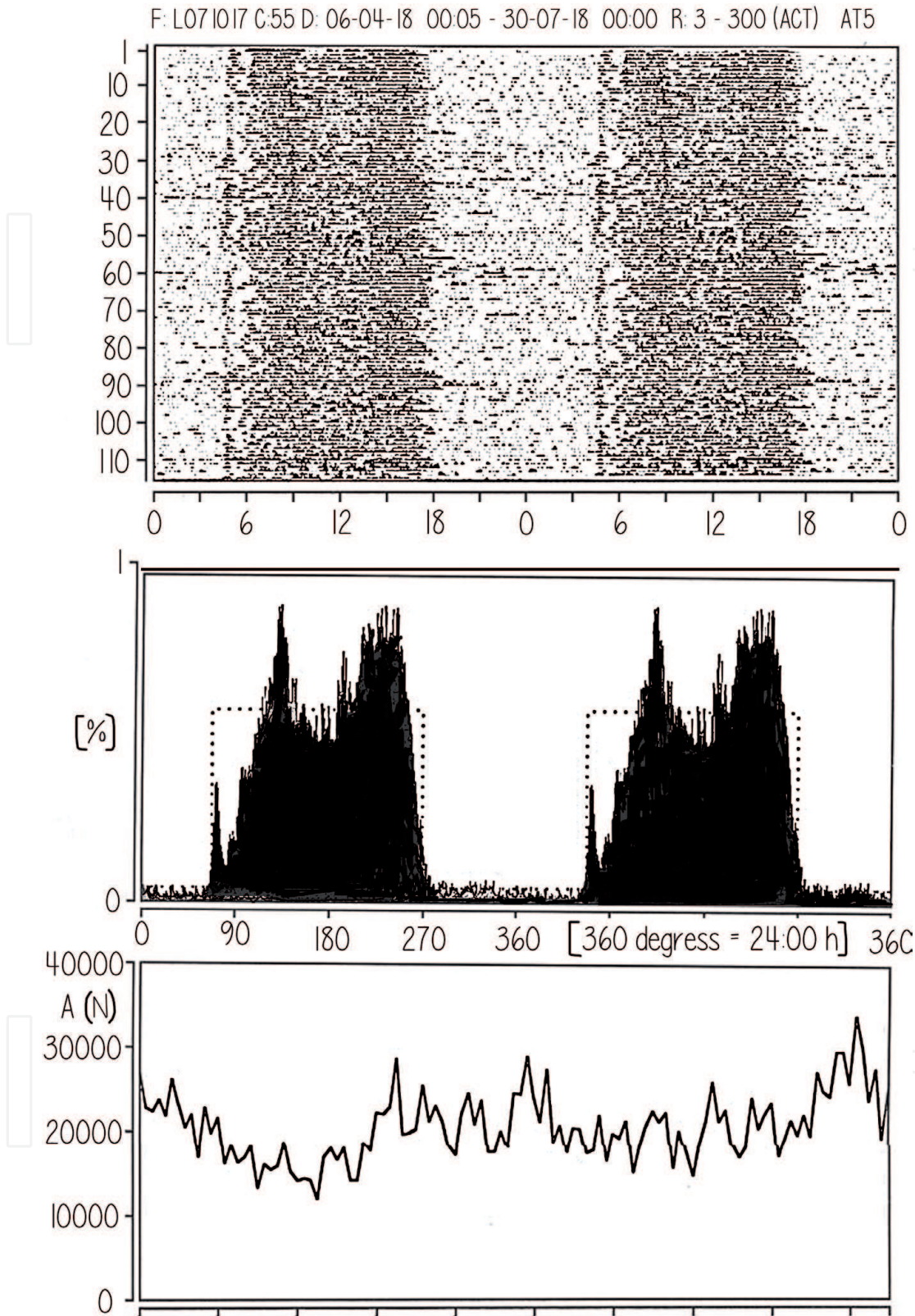
Figure 2.
Circadian rhythm of motor activity in the Mexican spider monkeys Ateles geoffroyi. The motor activity was recorded continuously and plotted as an actogram. This scheme shows the diurnal circadian pattern in this species.

functions and behavioral activities controlled by the circadian clock that can reper-cuss on mental health. Hence, the main goal of this chapter is to review and discuss the evidence that supports the influence of melatonin on circadian physiology

focusing on its modulatory effects on neurodevelopment and brain plasticity as well as on the importance of this indole for the treatment of neuropsychiatric diseases.

2. Circadian rhythms can be modulated by melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine) is a biogenic amine synthesized from tryptophan (**Figure 3**) that was first isolated and characterized by Aaron B. Lerner
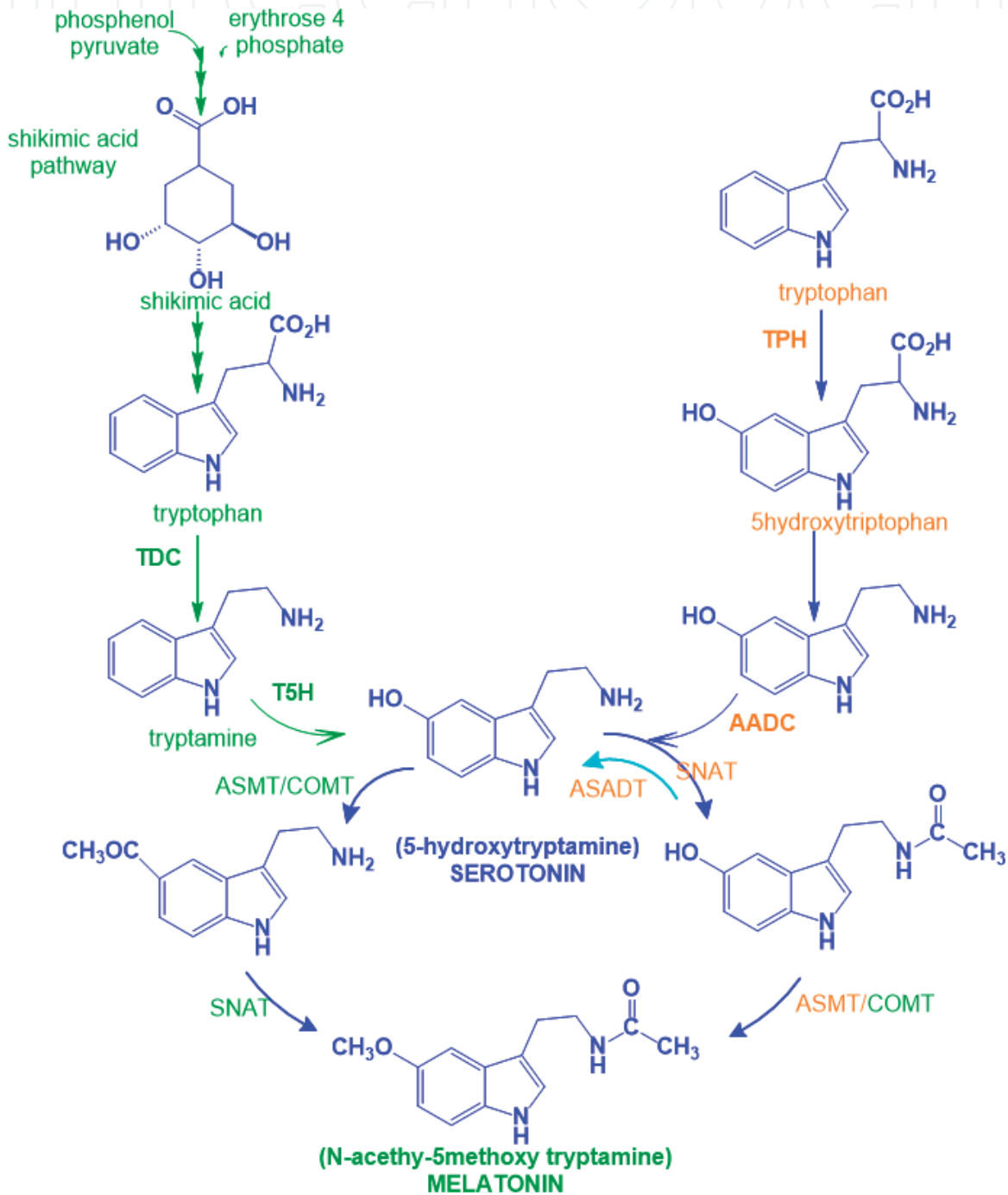
Figure 3.
Synthesis pathway of melatonin. The metabolic pathway for melatonin biosynthesis begins necessarily with tryptophan This synthesis consists of several enzymatic reactions; among them the hydroxylation by tryptophan hydroxylase (TPH) produces 5-hydroxytryptophan; in addition, serotonin is formed by the aromatic amino acid decarboxylase (AADC); at the end, N-acetylserotonin-O-methyltransferase (ASMT), produces melatonin.

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and coworkers in 1958, from more than 200,000 lyophilized bovine pineal glands. The amphiphilic nature of melatonin allows it to cross the cytoplasmic membrane and interact directly with intracellular proteins as calmodulin [7, 8] or nuclear receptors [9]. This indole can also bind to membrane receptors to trigger specific signaling pathways [10]. This variety of molecular targets distributed inside cells as soluble proteins and outside cells such as heptahelical receptors could explain the extensive participation of melatonin to modulate a great variety of key functions in cellular physiology.

As mentioned previously, circulating melatonin concentration oscillates following a circadian rhythm with a nocturnal peak in almost all studied species (**Figure 4**). This oscillation is regulated by light implying that the rhythm could be synchronized by the photoperiod, in the same manner as other functions [11]. The most ancient function of melatonin apparently is the protection against oxidative stress. Still, in animals, this indole regulates even complex behaviors such as daily activity and seasonal reproduction, some sleep properties, as well as retinal, hormonal, metabolic, and immune functions [12]. In contrast to non-mammalian vertebrates, pinealectomy in rat or mouse does not disrupt the circadian rhythmicity; instead, these animals retain most of their circadian rhythms, including the oscillating locomotor activity; however, a subtle uncoupling of several physiological functions occurs [13]. In mammals, the melatonergic system has only a secondary rank in the circadian system [14]. Apparently, the temporal signal produced by SCN is distributed to peripheral clocks by both neural pathways through the hypothalamic nucleus and the autonomous nervous system [15, 16], and endocrine pathways mediated mainly through melatonin from the pineal gland. An example of the latter is the requirement of melatonin signal in the maintenance of circadian activity in the *pars tuberalis* of adenohypophysis [17].
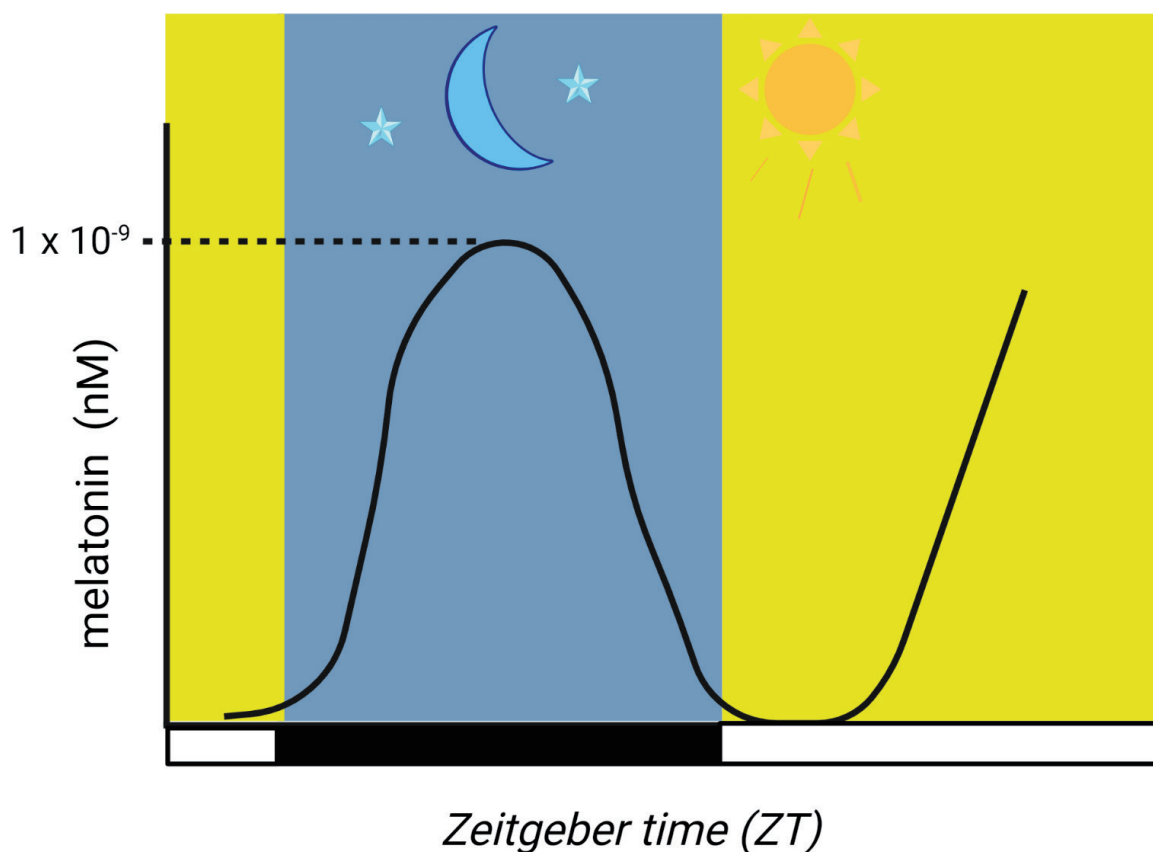

Figure 4.
Circadian rhythm of melatonin release. The hormone melatonin is released from the pineal gland in mammals at night. This molecule has been considered the signal of darkness to adjust the circadian system.

To address the role of melatonin as a synchronizer molecule, several experimental strategies have been developed. For example, the organisms are maintained under constant environmental conditions in which the circadian rhythms present a free-running period that could be shorter or longer than 24 h. In this condition, one stimulation with exogenous melatonin applied at different circadian times can induce a phase shift in the oscillation; this change can be a delay or an advance of the rhythm phase. Also, under the same constant environmental condition, a daily melatonin stimulus is applied at a specific external time, so the rhythm becomes adjusted with respect to the periodic stimulation. Both the period and the phase of the rhythms change and are synchronized by melatonin. In both cases, the conclusion is that melatonin is a synchronizer acting on the circadian pacemaker.

In all vertebrates, melatonin membrane receptors seem to be involved in both the phase shifts induced in the circadian oscillations and in the synchronization of the rhythms by injected or infused melatonin [18–20]. It has been proposed that the pathway activated by melatonin is dependent on the subtype of membrane receptors distributed in the SCN or in the pineal gland itself. In many non-mammalian vertebrates, melatonin receptors distributed in different tissues, including the SCN, seem to be involved in the transduction of the timing of circadian rhythms, but also in phase shifts and synchronization [20].

Melatonin shifts the phase of the locomotor activity rhythm and the firing rate of the mammalian SCN neurons. These actions can be mediated by MT2 receptors. The mammalian circadian pacemaker is sensitive to exogenous melatonin at the hours around day-night and night-day transitions [21, 22]. When melatonin is applied to male C3H/HeN mice at CT10, that is, two circadian hours before the onset of activity, the hormone induces dose-dependent phase advances [23]. This effect is significantly reduced by application of the selective MT2 antagonist 4P-PDOT. This antagonist also diminishes the melatonin-induced phase advances of the SCN neuronal firing rhythm in male Long-Evans rats [24]. In MT1 receptor-deficient mice, the application of melatonin at CT10 still produced phase advances [25]. A common example of circadian rhythms phase shift is the so-called jet lag induced by traveling across several time zones. Melatonergic agonists such as ramelteon and tasimelteon (nonselective MT1/MT2 agonists) have been used as therapeutic options for alleviating the sleep disturbances associated with this transient perturbation in the temporal organization of the circadian system [26].

Melatonin synchronizes the locomotor circadian rhythm in Long-Evans rats, Wistar rats, and the diurnal rodent *Arvicanthis ansorgei* following a daily stimulation procedure by injection or infusion of the indolamine [27–29]. Interestingly, in nocturnal rodents synchronized by melatonin, the activity onset is coincident with melatonin application, as expected considering that melatonin release is nocturnal; in contrast, in the synchronized diurnal species, melatonin application coincides with the beginning of the rest phase [30].

Even though pinealectomy does not induce apparent changes in the properties of most of the circadian rhythms in mammals, it has been observed that the decrease in melatonin levels affects some important circadian functions such as the sleep-wake cycle and triggers depressive-like symptoms; these disturbances have been improved with the administration of melatonin receptor agonists [31], suggesting that the role of this pleiotropic hormone in physiology might be underestimated. One important function of melatonin that can repercuss in the brain physiology is the modulation of neurogenic processes and circuit functioning as explained below.

3. The neuroplastic changes show circadian rhythms

Similarly, to the behavioral studies of primates' activity rhythms and their modulation by environmental variables, there are also studies about the regulation of molecular and cellular processes influenced by Zeitgebers that participate in the behavior. One example is the neurodevelopment in the hippocampus, which is the brain region where learning and memory are integrated [32]. This function plays a key role in the adaptation of the organism to the environment. Neurodevelopment implicates the formation of new neurons, cell migration, cell differentiation, and the formation of neuronal projections dendrites and axons as well as the formation of synaptic contacts that culminate in the establishment of neuronal connections that together constitute the structural network that underlies brain function.

In 1966, Altman found that new neuron formations occur in the adult brain, making a breakthrough in the concept of that times that new neuron formation occurred only at embryonic stages [33]. However, Altman, for the first time, demonstrated by immunohistology and autoradiographic technique the incorporation of 3H-thymidine into the DNA of cerebellar cells of rats at postnatal age [33]. In the last decade of the past century, further contributions to this field emerged, and it was clear that neurogenesis continues throughout the entire life at various locations in the brain such as the subventricular zone, the olfactory bulb, and the dentate gyrus of the hippocampus [34]. In an analogous manner to neurogenesis, dendrite and axonal formation as well as synaptic contact, establishment occurs during the entire life, making the brain a highly neuroplastic an adaptative organ.

Adult neurogenesis as well as neuroplasticity is conserved processes in all mammalian species studied so far including non-human primates and humans [35]. Both processes are mechanisms that allow the survival and the well adaptation of the organisms to environmental conditions. In this regard, melatonin, a phylogenetically conserved molecule, allows survival and adaptation acting as a free radical scavenger and enhancing the levels of antioxidant enzymes protecting the brain against stressful stimuli. Moreover, because the indolamine stimulates neurogenesis and new neuronal contact formation in the hippocampus, it makes the organism more competent for survival.

The evidence about circadian regulation of neurodevelopment in the adult brain was aroused by the observation that melatonin stimulates different stages of neurodevelopment and because the indolamine is synthesized according to the photoperiod and synchronized the internal activity with the environmental light. In this regard, melatonin synchronizes the sleep-wake cycle, the body temperature, the cortisol release, among other functions.

The adult brain presents neuroplastic changes that follows a circadian rhythm; for instance, the maximal amplitude of neuroplasticity occurs during the scotophase regardless of the activity pattern of the species (diurnal or nocturnal). In the hippocampal subgranular zone of murine adult, proliferation of immature neurons increases at the middle of the scotophase (*Zeitgeber Time* 18: *ZT*18) where the maximum amplitude of melatonin secretion occurs. By contrast, neuronal apoptosis decreases at that time having the maximal increase at the middle of the light time (*ZT*6). Interestingly, these rhythmic changes occur only in animals with functional melatonin MT1 and MT2 receptors [36].

In diurnal zebrafish, and in nocturnal mice, the stages of the cell cycle in stem cells of neurogenic niches show a circadian rhythm with nocturnal peak [37]. These rhythms correlate with the expression of Clock1 and Per1 in zebrafish [37] and with

Per2 and Bmal1 in mice [38]. These results suggest that cell proliferation is controlled by the clock genes in most mammalian species [39–41]; interestingly, melatonin can influence the level of clock gene expression [42] and the half-life of clock proteins by timing their degradation in the proteasome [43].

Neuroplastic changes in dendrites also follow a circadian pattern. In Siberian hamsters, the hippocampal dendritic structure of basilar dendrites of CA1pyramidal neurons revealed dendrite length increase that occurs during the dark phase [44]. Moreover, the number of branch points significantly increases during short days (8 h L: 16 h D), indicating a more complex dendritic arbor, while during long days (16 h L: 8 h D), the dendrites are longer. Administration of melatonin at the end of the light phase induces the nocturnal dendritic morphology in CA1 neurons within 4 h. In addition, in organotypic cultures of hippocampus incubated with melatonin 100 nM, dendrite formation in the hilar zone is evident after 6 h of incubation and increased formation of secondary and tertiary dendrites [45] (**Figure 5**). The changes in dendrite size and complexity are correlated with the increase in the expression of Per1 and Bmal1 in the hippocampus [46]. Hence, in short or long photoperiod schemes, the duration of endogenous melatonin release would change respecting the length of the dark phase, providing seasonal information to neurogenic niches [47].

Synaptogenesis, the main event by which neurons are connected, is also regulated by the circadian rhythms. Two approaches have been used to study synaptic formation: (1) structural studies in which immunostaining of synaptic proteins by specific antibodies was used to label dendrite spines the site where synaptogenesis takes place and electrophysiological approaches where long-term potentiation is studied (LTP). The former showed a circadian pattern reaching a maximum number or size of dendritic spines during the dark phase in the hippocampus and somatosensory cortex in mice [48, 49]. Moreover, increased synapses formation is observed in hippocampal organotypic cultures
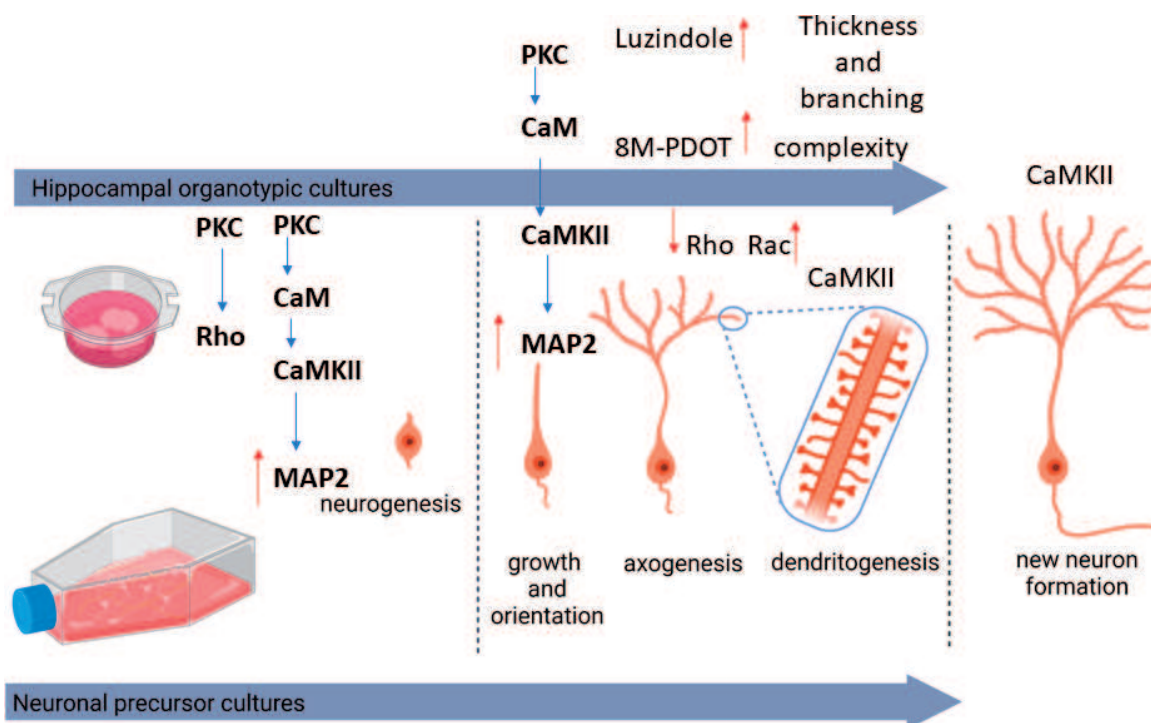

Figure 5.
Neurogenesis in hippocampus and neuronal precursor cells. The neurogenesis process has been studied in organotypic cultures and in isolated precursors obtained from the olfactory epithelium to determine the stimulatory effect of melatonin.

incubated with 100 nM melatonin and by staining with an anti-synapsin antibody, which labels synapsin a protein localized in the presynapsis [45]. Despite this information, studies in Siberian hamsters indicate a decrease in dendritic spine density during the dark phase in the dentate gyrus [44, 46]. Thus, it is necessary to study more deeply the rhythmicity of synapses formation and the factors that influence it.

On the other hand, electrophysiological studies have shown that synaptic strength measured through hippocampal LTP was more significant in magnitude and stability in slices obtained during the dark phase [50]. This pattern persisted even in constant darkness or in slices obtained at daytime and recording LTP at night; these results suggest an endogenous rhythm in synaptic plasticity that could persist *ex vivo* in the slices. Moreover, melatonin, perfused during the light phase, reduces the hippocampal LTP at a wide range of concentrations (0.01–100 µM) [51, 52]. In summary, these results suggest that hippocampal neuroplasticity is controlled by the light/dark cycle and by melatonin. Other evidence concerning melatonin's role as neuronal modulator has been found in neuronal stem cells obtained from the olfactory epithelium, as mentioned in the next section.

4. Melatonin stimulatory effects on structural neuroplasticity in a translational model

Current studies indicate that olfactory neuronal precursors are a subrogate model of the central nervous system to study neurotransmitter receptors expression, enzymes involved in neurotransmitter synthesis as well as the neurodevelopment in the adulthood.

Olfactory neurons have a common ectodermal embryonic origin with the CNS neurons and are derived from embryonic placodes and the neural crest, which are structures analogous to the neural tube [53, 54].

Gene expression profiles of olfactory neuronal precursors are similar to mesenchymal stem cells and can be differentiated into mature olfactory neurons and other types of neurons such as dopaminergic neurons [55, 56]. The expression of hundreds of genes such as CNS neurons has been shown in olfactory neuroepithelial cells. Some of these are the pituitary adenylate cyclase-activating peptide and the glutamate receptor, among others [57–59]. Moreover, in postmortem samples obtained from Alzheimer's disease patients, paired helical filaments of tau protein and amyloid-β plaques similar to those found in cortical and subcortical neurons have been described in olfactory neuroepithelial cells characterized by cytokeratin-18 expression reflecting its stromal epithelial cell nature, as well as in olfactory neurons characterized by III β-tubulin expression [60, 61]. Recently, neuronal precursors were obtained from alive patients with Alzheimer's disease diagnosis and demonstrated the paired helical filaments, as well as increased levels of tau total and phospho-tau supporting that olfactory neuroepithelial cells are a mirror model that reflects molecular changes produced in the CNS and useful to study different stages of neurodevelopment in samples obtained from alive patients [62].

In this regard, it was demonstrated that spontaneous axogenesis occurs in olfactory neuronal precursors derived from a clone obtained by unlimited dilution from a female of 55 years with no psychiatric history. Twelve percent of these cells maintained in primary culture the ability to form axons. In the presence of melatonin, axonal formation augmented by 15% in the primary cultures of olfactory neuronal precursors [63].

In addition to these observations, spine and new neuron formation in a clone of human olfactory neuronal precursors stimulated by melatonin was demonstrated. Spines were labeled with Phalloidin-Rhodamine and an anti-spinophilin antibody and counted. The prelaminar results showed that melatonin increases spine formation in primary cultures of human olfactory neuronal precursors. Moreover, neurogenesis measured as clusters of proliferating neuronal precursors has been observed in the presence of 100 nM melatonin (manuscript in preparation). Altogether, evidence supports that melatonin stimulates three important stages of neurodevelopment, neurogenesis, spine formation, and axogenesis.

5. Chrono-disruption in neuropsychiatric diseases

In addition to natural *Zeitgebers* and masking factors, certain pathologies and the pharmaceuticals used to treat them can also alter activity patterns. It is well known that disruption of circadian cycles is a common feature in neuropsychiatric diseases. Among these, alterations in the sleep-wake cycle, core body temperature, appetite, and hormonal release cycles such as the cortisol secretion have been described in patients with neuropsychiatric alterations such as Alzheimer disease, bipolar disorder, major depression, and schizophrenia among other diseases. Importantly, all these functions are cyclically modulated by melatonin and in neuropsychiatric patients, the amplitude of melatonin secretion peak is blunted.

In human subjects, the pattern of motor activity in unmedicated schizophrenia patients and healthy subjects had been study to disclose whether the pattern was affected by treatment with typical and atypical antipsychotics (haloperidol and risperidone). Twenty unmedicated schizophrenic patients wore a wrist actigraph that recorded activity at 1-min intervals for five days. The activity pattern of patients and healthy subjects was compared; then, the patients were randomly assigned to treatment with low-dose haloperidol or risperidone, and the effect of treatment on the activity was tested. Untreated patients were less active during morning, evening, and late-night periods compared with controls. Both haloperidol and risperidone induce significant effects on activity level (this effect was more prominent with haloperidol). The results suggest that unmedicated schizophrenic patients exhibit abnormally low levels of motor activity, which persists with antipsychotic treatment, even though symptoms improve. Future studies should clarify whether motor disturbances are a primary effect of the illness or related to the lifestyle effects [64].

In addition, some antidepressants flatten the amplitude of melatonin secretion, contributing to the alterations of biological rhythms inherent to major depression. Thus, it can be suggested the use of melatonin as a therapeutical adjuvant to regulate biological rhythms such as the sleep/wake cycle.

Recently, we explored if neuroplasticity is altered in schizophrenia. By using the translational experimental model of olfactory neuronal precursors, we found that these cells derived from a patient with schizophrenia were unable to form axons spontaneously. However, in the presence of melatonin, these cells formed axons with the same rate as cells derived from a healthy subject with no psychiatric history [63]. Thus, data suggest that besides the inherent disruption of biological rhythms in schizophrenia patients and drug administration, they also have impaired axonal rhythm formation during adulthood that can be restored by melatonin.

6. Importance of time administration of drugs in the treatment of neuropsychiatric diseases

As mentioned before, human beings have a rhythmic expression in their physiology and behavior. In homeostasis states, this endogenous rhythmicity is synchronized by cyclic environmental factors. This coupling provides several advantages: anticipating cyclical changes in the background and facilitating the organism's adaptation to its environment. This rhythmicity has systems that allow measuring the passage of time, and it is regulated by environmental signals (exogenous) that act as external synchronizers. These rhythms oscillate approximately every 24 h, and among these, the most important is the light-dark cycle or cycle circadian. This concerted, internal, and external rhythmic expression is essential to maintain a healthy state. There is strong evidence that supports the idea that the disruption or chrono-disruption of this adaptive mechanism is detrimental to health and has, among other consequences, sleep disorders, which can lead to cognitive deterioration. It has also been associated with an increased risk of cardiovascular disease, hypertension, metabolic conditions such as diabetes, cancer, obesity, and affective disorders such as anxiety and depression, increasing the prevalence of neuropsychiatric disorders such as schizophrenia and major depression.

The synchronization of circadian rhythms with pharmacotherapy is crucial for neuropsychiatric and affective disorders treatment since it is about combining the maximum benefit with the minimum time complexity of the treatments.

Adequate coordination between drug administration schedules to obtain an optimal therapeutic response has been little explored and currently represents a challenge for chrono-pharmacology.

Desynchronization between the times of administration and the potential pharmacological effects could be one of the reasons why a high percentage of patients with major and bipolar depression (MD) are resistant to treatment, as well as the chronic recurrence of depressive and seasonal disorders. Chronotherapeutic strategies that reset the internal clock may have a specific advantage for treating depression and other mental disorders.

For instance, seasonal affective disorder (SAD) is a sub-type of depression in which individuals experience depressive symptoms and show hypersomnia only in the winter months, in which the period of darkness is more extended than at other times of the year. In a pioneering study, Rosenthal and coworkers [65] found that treatment with bright environmental light suppresses the endogen melatonin secretion and reverses the winter depressive symptoms of patients with SAD. In contrast, light too dim to suppress endogen melatonin is therapeutically ineffective.

This same paper described the antidepressant effects of phototherapy in eight SAD patients by oral melatonin administration. However, in another study with 19 SAD patients, the authors did not find any therapeutic difference between the atenolol, a beta-adrenergic blocker, which inhibits melatonin secretion, and placebo. In contrast, research with seven SAD patients showed that the antidepressant effects of phototherapy were not photoperiodic and appeared to be independent of melatonin suppression. Authors conclude that melatonin can mediate the effects of shortening days on the winter symptoms of SAD and that the modification of melatonin secretion by bright light mediates its antidepressant effects and gives evidence that melatonin secretion may be abnormal in SAD [65].

Multiple factors can disrupt this chronicity because of imbalances in the sleep-wake cycle. Disruption of circadian cycles has also been associated with affective disorders.

Depression disorders are characterized by a broad range of symptoms, including altered mood, loss of cognitive functions, and recurrent thoughts of death or suicide. The relationship between chrono-disruption and the etiology of depression is not yet clear. However, evidence suggests that existing pharmacotherapies such as lithium and antidepressants such as melatonin and agomelatine act on the circadian system.

Although it is known that melatonin is a mediator of photoperiodic changes on seasonal rhythms in animals, a gradual increase in circulating levels of melatonin occurs after lights off, reaching its maximum around the middle of the dark phase. There is contradictory evidence about the antidepressant effect of melatonin itself. We found that the melatonin administration in mice at two *Zeitgeber times* (ZT = 0 lights on; 12:12 L/D), 1 h before the beginning (ZT11) and at the middle (ZT18) of the dark phase after either a single or a three-dose treatment, produces a robust antidepressant-like effect in the tail suspension and the forced swimming tests. When a single dose of melatonin (4 mg/kg) was administered at ZT 11 produced an antidepressant-like effect in two paradigms. However, when melatonin was administered at ZT 18, it was ineffective in the forced swimming test. Required a higher dose of melatonin (16 mg/kg) to observe their antidepressant effect in the tail suspension test. In contrast, repeated doses of melatonin (ZT 18, ZT 11, and ZT 18) were necessary to produce the antidepressant effect in the forced swimming test. These results highlight the importance of the timely administration of melatonin could improve its antidepressant-like effect [66].

Agomelatine is an antidepressant that acts as an agonist on the melatonin receptors and as a 5HT2C receptor antagonist. Several studies suggest that the antidepressant effect caused by agomelatine results from the resynchronization of circadian rhythms that are disturbed in depressed patients ameliorating symptoms of depression. In contrast to other antidepressants, this has shown low relapse rates upon discontinuation and high tolerability. Furthermore, agomelatine treatment improves the amplitude of the circadian (rest/activity) sleep/wake cycle and diminishes the depression and anxiety symptoms in comparison with sertraline treatment [67].

There is strong evidence about the association between sleep disturbances and depression; in depressive disorder (MDD), the desynchronization of circadian rhythms occurs, producing disturbed sleep and insomnia, and these symptoms improve markedly with melatonergic (MT1 and MT2) and 5HT2C agonist treatment such as melatonin and agomelatine, which act as modulating the circadian rhythmicity.

The foregoing gives evidence of the disruptions of the sleep-wake cycle (sleep architecture and timing) and residual symptoms may prevent the attainment of high-quality remission and delay recovery from MDD.

Benedetti and coworkers studied the effect of morning light therapy or placebo combined with the serotonin reuptake inhibitor citalopram in treating patients affected by a major depressive episode without psychotic features. They found that the combination of this antidepressant and light treatment was more effective than citalopram alone or placebo in the treatment of major depression, administered with an optimized timing of administration, and low-intensity light treatment that significantly hastened and potentiated the effect of citalopram. This evidence provides the clinical psychiatrists with an augmenting strategy, effective and devoid of side effects [68].

Alterations in circadian rhythmicity have been little studied in patients with schizophrenia, in which sleep disorders are common, with an 80% prevalence that often responds to circadian disruption.

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This study showed that the variability of sleep-wake time is notably more significant and more remarkable in the schizophrenia group than in the people without the disorder [69].

In addition, polysomnography studies have shown that these patients present a higher sleep latency, diminished total sleep time, lower efficiency, more interruptions, a shorter duration, and latency of REM dreams, as well as a lower proportion of slow-wave sleep than people without this condition. Also, deficit sleep spindles in schizophrenia people could be an endophenotype of this disorder.

In a study of rest activity, a cohort of patients with schizophrenia matched with healthy subjects, Wulff and coworkers [69] showed that there is clear evidence of sleep and circadian rhythm disruption in schizophrenia patients, over half the cohort, tested showed severe circadian misalignment, including the melatonin cycle.

Compared rest-activity patterns in a cohort of patients with schizophrenia with matched healthy unemployed controls showed significant sleep/circadian disruption in all 20 patients studied. Of these, half showed severe circadian misalignment in sleep-wake and melatonin cycles, demonstrating that abnormal entrainment of the circadian system is prevalent in schizophrenia.

Although the results are not conclusive yet and more research is needed in this regard, chronotherapy is a relatively recent proposal to optimize pharmacological treatments based on the biological clock to maximize the pharmacological response or produce adjustments when there is a desynchronization in the biological functions that are affected in illnesses, including mental disorders. Therefore, it is necessary to adequately coordinate medication administration schedules to obtain the maximum pharmacological results and increase treatment adherence.

7. Conclusion

Evidence presented in this chapter indicates that neuroplasticity is modulated by an external *Zeitgeber*, the photoperiod, and synchronized by melatonin which is an endogenous synthesized molecule during the dark phase. Notably, functions such as neurogenesis, dendrite, axonal, and synaptogenesis are upregulated during the dark phase of the photoperiod and by 100 nanomolar concentrations of melatonin, which is the concentration reached in the cerebrospinal fluid during the dark phase of the photoperiod. Nowadays, neuroplasticity is considered an important tool for the treatment of neuropsychiatric diseases to repair damaged circuitry in the brain of these subjects. Therefore, since melatonin can increase all the stages of neuroplasticity at pharmacological concentrations, it is possible for the use of this indolamine as an adjuvant for the treatment of neuropsychiatric diseases where chrono-disruption is one of the main symptoms evidenced by alterations in the sleep/wake cycle, the motor activity and the pineal secretion of melatonin among other rhythms important for the good quality of life.

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Conflict of interest

The authors declare no conflict of interest.

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