



REVIEW ARTICLE

Circadian modulation of neuroplasticity by melatonin: a target in the treatment of depression

Correspondence Dr Gloria Benítez-King, Laboratorio de Neurofarmacología, Subdirección de Investigaciones Clínicas, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, Calzada México-Xochimilco 101, San Lorenzo Huipulco, Tlalpan, Ciudad de México 14370, Mexico. E-mail: bekin@imp.edu.mx

Received 3 July 2017; **Revised** 15 February 2018; **Accepted** 21 February 2018

Marcela Valdés-Tovar^{1,*}, Rosa Estrada-Reyes^{2,*}, Héctor Solís-Chagoyán¹, Jesús Argueta¹, Ana María Dorantes-Barrón², Daniel Quero-Chávez¹, Ricardo Cruz-Garduño¹, Montserrat G Cercós³, Citlali Trueta³, Julián Oikawa-Sala¹, Margarita L Dubocovich⁴  and Gloria Benítez-King¹ 

¹Laboratorio de Neurofarmacología, Subdirección de Investigaciones Clínicas, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, Ciudad de México, Mexico, ²Laboratorio de Fitofarmacología, Dirección de Investigaciones en Neurociencias, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, Ciudad de México, Mexico, ³Departamento de Neurofisiología, Dirección de Investigaciones en Neurociencias, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, Ciudad de México, Mexico, and ⁴Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo (SUNY), Buffalo, NY 14214, USA

*These authors contributed equally to this work.

Mood disorders are a spectrum of neuropsychiatric disorders characterized by changes in the emotional state. In particular, major depressive disorder is expected to have a worldwide prevalence of 20% in 2020, representing a huge socio-economic burden. Currently used antidepressant drugs have poor efficacy with only 30% of the patients in remission after the first line of treatment. Importantly, mood disorder patients present uncoupling of circadian rhythms. In this regard, melatonin (5-methoxy-N-acetyltryptamine), an indolamine synthesized by the pineal gland during the night, contributes to synchronization of body rhythms with the environmental light/dark cycle. In this review, we describe evidence supporting antidepressant-like actions of melatonin related to the circadian modulation of neuroplastic changes in the hippocampus. We also present evidence for the role of melatonin receptors and their signalling pathways underlying modulatory effects in neuroplasticity. Finally, we briefly discuss the detrimental consequences of circadian disruption on neuroplasticity and mood disorders, due to the modern human lifestyle. Together, data suggest that melatonin's stimulation of neurogenesis and neuronal differentiation is beneficial to patients with mood disorders.

LINKED ARTICLES

This article is part of a themed section on Recent Developments in Research of Melatonin and its Potential Therapeutic Applications. To view the other articles in this section visit <http://onlinelibrary.wiley.com/doi/10.1111/bph.v175.16/issuetoc>

Abbreviations

BDNF, brain-derived neurotrophic factor; CA, cornus ammonis; CaM, calmodulin; CMS, chronic mild stress; FST, forced swimming test; LAN, light at night; LL, constant light; MDD, major depression disorder; SCN, suprachiasmatic nucleus; TST, tail suspension test; ZT, Zeitgeber Time

Introduction

According to the latest version of the Diagnostic and Statistical Manual of Mental Disorders from the American Psychiatric Association (DSM-5, 2013), mood disorders are defined as a spectrum of neuropsychiatric disorders characterized by disturbances in the emotional state such as prolonged and persistent periods of extreme sadness or extreme happiness. They comprise bipolar disorder, anxiety disorder, seasonal affective disorder, as well as minor, mild and major depression disorder (MDD). Depression is characterized by the loss of interest and pleasure (anhedonia), the lack of energy (anergia), loss of appetite and alterations in sleep patterns that decrease the patients' occupational and social functioning. The aetiology of MDD is multifactorial with genetic, environmental and neuroendocrine factors, all participating in its development.

One important feature of mood disorders is the uncoupling of circadian rhythms. Patients with seasonal affective disorder, MDD and bipolar disorder show a misalignment in the sleep/wake cycle. Also, core body temperature, appetite and hormonal release cycles are altered, including advance of **melatonin** secretion onset in some patients and blunted rhythms of clock genes expression in the brain (Beck-Friis *et al.*, 1985; Sou tre *et al.*, 1989; Landgraf *et al.*, 2014). Importantly, both low melatonin doses and bright light exposure entrain the sleep–wake cycle and increase the amplitude of the melatonin secretion peak at night (Emens and Burgess, 2015). Many different strategies aimed at counteracting circadian misalignment have been beneficial for the clinical management of mood disorders.

In mammals, the circadian system regulates the timing of physiological and behavioural processes. The hypothalamic biological clock, the suprachiasmatic nucleus (SCN), is considered the master pacemaker. The SCN is synchronized by environmental cues, such as the light/dark cycle, and regulates the circadian rhythm of melatonin synthesis by the pineal gland. Pineal melatonin synthesized during the dark phase is released into the CSF of the third ventricle from which it diffuses to different regions of the brain to signal the environmental photoperiodic changes. Cellular circadian oscillators that control physiological functions might in turn be regulated by melatonin (see Hardeland, 2013).

Melatonin modulates circadian rhythms through signalling pathways coupled to the melatonin receptors, **MT₁** and **MT₂** (Hardeland, 2013; Liu *et al.*, 2017). Activation of the **MT₂** receptor phase advances the circadian rhythm of neuronal firing in SCN slices (Hunt *et al.*, 2001), although a role for the **MT₁** receptor cannot be excluded (Liu *et al.*, 1997). The **MT₁** receptor appears to be involved in melatonin-mediated phase advances of circadian rhythms in the mouse *in vivo* (Dubocovich *et al.*, 2005). Both the **MT₁** and **MT₂** receptors are involved in mediating anhedonic and anxiety-like behaviours (Liu *et al.*, 2017). Recently, melatonin was reported to increase the expression of the clock genes *Per1* and *Per2*, which play a critical role in circadian clock resetting (Kandalepas *et al.*, 2016).

In MDD patients, plasma levels of melatonin are decreased. This is related in part to a persistent brain inflammatory response mediated by the infiltration of immune cells through the blood brain barrier and increased

levels of soluble pro-inflammatory proteins (Anderson, 2017). Decreased levels of melatonin can also be related to a gene variant that codifies for N-acetylserotonin O-methyltransferase, a key enzyme in the melatonin biosynthesis that has low mRNA expression and low activity in bipolar disorder (Etain *et al.*, 2011). In addition, patients with either MDD or bipolar disorder may have lower responses to melatonin due to a single nucleotide polymorphism located near the *MTNRIA* gene for the **MT₁** receptor (Demirkan *et al.*, 2016).

Another important feature in patients with MDD is a decrease in cognitive functions associated with a reduction in hippocampal volume (Drevets *et al.*, 2008). Hippocampal atrophy implies an overall impairment of neuroplastic processes, which in preclinical studies can be modulated by melatonin. Additionally, in MDD, little attention has been paid to alterations in neuroplasticity due to photoperiod changes, which are environmental cues that entrain circadian rhythms. Therefore, this review focuses on evidence supporting the antidepressant effects of melatonin in relation to the light/dark cycle, and its modulatory role in hippocampal neuroplasticity.

The neurotrophic and glutamatergic hypotheses in the aetiology of major depression: importance for neuroplasticity

In 2000, the neurotrophic hypothesis of MDD was put forward, in place of the monoaminergic hypothesis and highlighting the importance of hippocampal neuroplasticity for the treatment of this disorder. This hypothesis postulates that hippocampal neurogenesis is impaired in depression due to decreased amounts of neurotrophins such as **brain-derived neurotrophic factor** (BDNF), causing a decrease in neuronal survival and alterations in the neuronal connections. In support of this hypothesis, a reduction in the hippocampal volume has been observed in patients with MDD together with decreased levels of BDNF. Also, chronic administration of antidepressants increases BDNF expression in the prefrontal cortex and hippocampus. Importantly, the selective **serotonin reuptake** inhibitors (SSRIs) besides their antidepressant effects, also stimulate neuroplasticity (Castren and Rantamaki, 2010).

Recent evidence showed that the glutamatergic system is also involved in the aetiology of MDD disease and that **NMDA receptor** antagonists used as antidepressants enhance neurogenesis in the prefrontal cortex and the hippocampus in rodents (Hillhouse and Porter, 2015). High levels of **glutamate** both in plasma and in CNS structures have been described in MDD patients (Hashimoto, 2009). High concentrations of glutamate in the CNS induce receptor hyperactivation, particularly of the ionotropic NMDA receptors which increase intracellular Ca^{2+} , leading to neuronal excitotoxicity and cellular death. Also, glutamate inhibits BDNF signalling and, as a consequence, neurogenesis. Melatonin exerts neuroprotective actions by counteracting the NMDA-mediated excitotoxic effects of glutamate, including the impaired BDNF signalling and cell death (Bavithra *et al.*, 2015). Exogenous melatonin can

differentially modulate glutamate release in CNS structures in rodents (Evely *et al.*, 2016), suggesting it might balance the disruption in the glutamatergic system in patients with mood disorders. Together, these data suggest that melatonin may increase neuroplasticity in the CNS acting on the glutamatergic system.

Antidepressant-like actions of melatonin in animal preclinical studies and clinical studies in humans

Behavioural tests in animals have been a useful tool to study antidepressant effects of drugs and their biochemical mechanisms. **Agomelatine**, an agonist at MT₁ and MT₂ receptors, was the first melatonin receptor ligand showing antidepressant-like activity in animal drug screening tests (Overstreet *et al.*, 1998). Soon it was discovered that its mechanism of antidepressant action also involved blockade of **5-HT_{2C}** receptors, with efficacy as a modulator of the monoaminergic system including enhancement of dopaminergic neurotransmission (Chenu *et al.*, 2013). In fact, the discovery that agomelatine had antidepressant effects in humans prompted preclinical research to validate the melatonin antidepressant effects.

The antidepressant-like effects of melatonin were demonstrated with the forced swimming test (FST), which is considered the gold standard of the antidepressant drug screening tests. Also, the tail suspension test (TST) and the chronic mild stress (CMS) test have provided evidence for the antidepressant-like actions of melatonin. Both FST and TST are learned helplessness paradigms where animals are exposed to unpredictable and uncontrollable stress, subsequently developing coping deficits for aversive but escapable situations. In male Swiss mice maintained under a 12:12 h light/dark cycle, the immobility time in the TST was reduced by the acute administration of melatonin (Mantovani *et al.*, 2003). This effect appears to be mediated through an interaction with NMDA receptors and the **L-arginine-NO** pathway. In contrast, acute administration of melatonin (2.5–10 mg·kg⁻¹) failed to induce an antidepressant-like effect in mice subjected to the FST for the first time. However, daily administration of melatonin prior to the swimming test significantly reduced the immobility time in the FST (Raghavendra *et al.*, 2000). On the other hand, CMS paradigms are based on the fact that chronic stress contributes to trigger depression in humans in a similar way that exposure to unpredictable stressors elicits altered behaviours in rodents that could be counteracted with antidepressant drugs. Moreover, these paradigms induce high basal **corticosterone** levels, which are reversed by **imipramine** and melatonin (Detanico *et al.*, 2009).

The antidepressant actions of melatonin have been related to the activation of melatonin receptors. The administration of the non-selective and competitive MT₁/MT₂ receptor antagonist **luzindole** to wild-type mice reversed melatonin's antidepressant-like activity in the FST (Micale *et al.*, 2006). In contrast, mice lacking MT₁ receptors display increased behavioural despair in the FST when compared with wild-type mice (Weil *et al.*, 2006). Also, several studies

suggest a hypofunction of the GABAergic system in depression and therefore administration of **GABA** agonists should produce antidepressant effects. In this regard, melatonin has been shown to increase the number of **GABA_A** receptors in rat brain suggesting this up-regulation may contribute to its antidepressant-like action.

In summary, there is sound evidence for the anti-stress and antidepressant-like actions of melatonin, suggesting its interaction with several neurotransmitter systems, including the GABAergic, serotonergic (Micale *et al.*, 2006), glutamatergic and nitroergic systems (Mantovani *et al.*, 2003), as well as the modulation of the hypothalamic–pituitary–adrenal axis (Detanico *et al.*, 2009).

Current clinical studies do not allow clear conclusions regarding melatonin effects as an antidepressant in humans. Most research has used melatonin in humans to alleviate sleep disorders associated with depressed mood (Serfaty *et al.*, 2010). However, patients participating in these clinical trials involve diverse psychiatric diagnoses making comparisons and evaluation of melatonin effectiveness as antidepressant in humans difficult (De Crescenzo *et al.*, 2017). A few clinical studies using better controlled variables and a larger number of patients support the use of melatonin to alleviate the symptoms associated with mood disorders (Beck-Friis *et al.*, 1985; Garzón *et al.*, 2009; Madsen *et al.*, 2017). However, carefully controlled and double-blind studies are needed to fully understand the effectiveness of melatonin in mood disorders either alone or as co-adjuvant to improve mood.

The hippocampus: a neuroplastic brain structure as a target for melatonin antidepressant-like actions

The human limbic system appears to be the main brain area affected in mood disorders (Figure 1). Brain imaging studies show structural abnormalities including decreased volumetric size in the prefrontal cortex and the hippocampus in these patients. The hippocampus is the major site of action for typical and atypical antidepressants and the structure where cognitive functions such as memory and learning are integrated (Drevets *et al.*, 2008). At the cellular level, structural hippocampal alterations are associated with the loss of subicular dendrites and their arborizations, and diminished neurogenesis in the dentate gyrus. At the behavioural level, the alterations in the hippocampal formation are associated with decreased adaptive responses manifested as a poor social integration and deficits in cognition and memory (Treadway *et al.*, 2015).

Preclinical evidence has shown that the hippocampus is a main target for melatonin actions (Figure 1), protecting this structure from damage caused by oxidative stress or ischaemia. Also, it promotes dendrite ramifications in cortical pyramidal neurons in rats exposed to toluene (Pascual and Bustamante, 2010) and prevents the loss of neurons in the cornu ammonis (CA)1 and CA3 hippocampal regions in pinealectomized rats (De Butte and Pappas, 2007).

Neuroplasticity is a complex process by which the neurons form intricate networks. It includes the formation of new neurons (neurogenesis), their differentiation

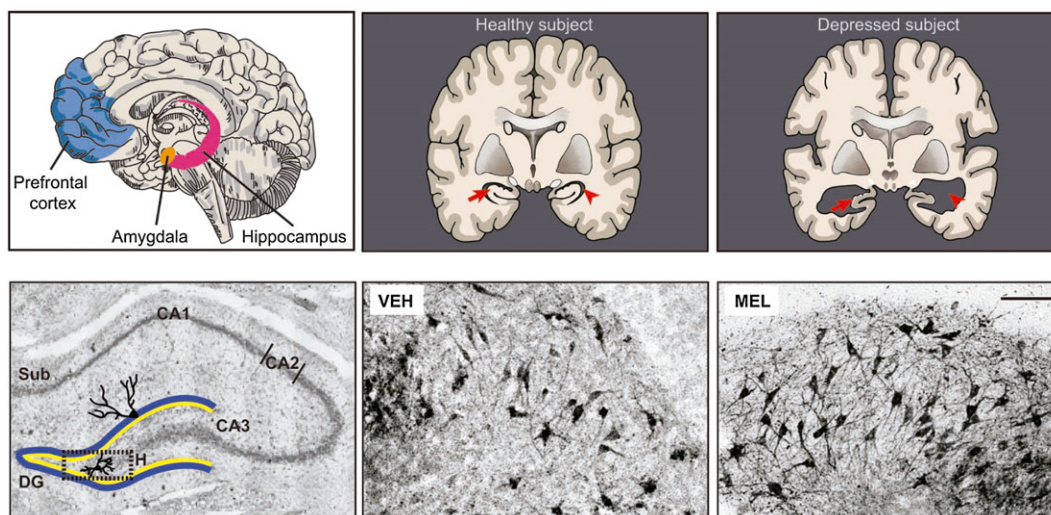


Figure 1

Potential targets for melatonin antidepressant actions. The prefrontal cortex, the amygdala and the hippocampus are altered in mood disorders. In rodents, these brain structures are targets for melatonin actions. In upper panel, schemes of the brain of depressive subjects show that the volume of the hippocampus (red arrows) is decreased and the lateral ventricles (red arrowheads) are enlarged in comparison with healthy subjects. Left lower panel shows the hilar zone of the rat hippocampus (H, dotted square), and the trisynaptic circuitry formed by the subiculum (Sub), the dentate gyrus (DG), and the CA1, CA2 and CA3 regions (Nissl stain). Amplifications of the hilar zone of hippocampal organotypic slices incubated for 6 h with the vehicle (VEH) or 10^{-7} M melatonin (MEL) are shown in the lower middle and right panels. Dendrites were immunodetected with a MAP2 antibody followed by a secondary antibody coupled to biotin-avidin-peroxidase. The anti-MAP2 antibody stains the soma and the dendrites. Also, melatonin prevents apoptosis (manuscript in preparation). Therefore, hippocampal slices incubated with melatonin showed an increased number of immunopositive cells. Scale bar: 100 μ m (Domínguez-Alonso *et al.*, 2012).

(axogenesis and dendritogenesis) and the establishment of proper connectivity into neural circuits (synaptogenesis) allowing the survival and the good adaptation of the organism to the environment. In rodents, melatonin stimulates all stages of neuroplasticity. In particular, the indolamine stimulates neurogenesis in the dentate gyrus in pinealectomized rats (Rennie *et al.*, 2009) and increases neuronal survival in C57BL/6 mice (Ramirez-Rodriguez *et al.*, 2009). Also, wheel running activity in combination with melatonin treatment stimulates neurogenesis in adult C3H/HeN mice (Liu *et al.*, 2013). Additionally, exogenous melatonin administration may elicit neurogenesis in sleep-deprived mice.

Melatonin is also known to stimulate dendritogenesis and synaptogenesis in the hippocampus. These processes are disrupted by chronic psychosocial stress as well as in depression (Kendler *et al.*, 1999) and can be reversed by antidepressants. In this regard, in newly formed neurons in the dentate gyrus and in differentiated hilar neurons in cultured hippocampal organotypic slices, melatonin enhanced dendrite formation and the number of synapses after 6 h of incubation (Domínguez-Alonso *et al.*, 2012) (Figure 1). Moreover, melatonin increased axonal formation in cultured rat hippocampal neurons (Liu *et al.*, 2015), and recently, we reported that melatonin enhances both axonal and synapse formation as well as extrasynaptic secretion in human olfactory neuronal precursors. Together, this evidence indicates that melatonin induces neuroplastic changes in the hippocampus.

The mechanism(s) by which melatonin modulates neuroplastic responses in the hippocampus involves

activation of melatonin receptors that have been localized in the dentate gyrus, CA3 and CA1 regions as well as in the subiculum. Activation of MT_1 and MT_2 receptors modulates cell proliferation in the subgranular zone of the dentate gyrus (Fredrich *et al.*, 2017). The involvement of MT_1 and MT_2 receptors in axonal formation in human olfactory neuronal precursors and in dendrite formation in organotypic hippocampal slices was recently reported by our group. In addition, melatonin induced dendrite formation by increasing **calmodulin** (CaM) availability and through the activation of **CaM-Kinase II**, **PKC** and **ERK1/2** (Domínguez-Alonso *et al.*, 2015). Relevant for neuroplasticity is the **Akt/GSK-3 β /CRMP-2** cascade that is involved in axogenesis and can be triggered by melatonin (Liu *et al.*, 2015). Importantly, melatonin has neuroprotective effects mediated by its antioxidant action as a free radical scavenger. In this regard, many *in vivo* and *in vitro* bioassays have been used to increase the oxidative status of brain tissues and to test the antioxidant protective effects of melatonin.

It is important to mention that, in addition to improving neuroplasticity in the hippocampus, melatonin attenuates the cognitive and memory deficiencies caused by sleep deprivation and ischaemia reperfusion (Zhang *et al.*, 2013). Also, melatonin receptors are involved in modulating mood behaviour. Thus, genetic deletion of the MT_2 receptor but not the MT_1 receptor in C3H/HeN mice induced anhedonic behaviour and decreased social interaction while increasing anxiety-like behaviours (Liu *et al.*, 2017). Conversely, this genetic deletion blocked the antidepressant effects induced by the competitive MT_1/MT_2 receptor antagonist luzindole

(Sumaya *et al.*, 2005). Further research is needed to fully understand the underlying mechanisms by which melatonin modulates behaviour.

Neuroplasticity shows a circadian rhythm: modulatory role of melatonin

The antidepressant effect of bright light in patients with seasonal affective disorder supports the importance of circadian rhythm entrainment in the treatment of MDD (Golden *et al.*, 2005). Preclinical studies have shown that neuroplastic changes in the adult brain follow a circadian rhythm and are also influenced by the light/dark cycle. In most cases, the maximum amplitude of neuroplastic rhythms is observed during the dark phase of the light/dark cycle, regardless of the activity pattern of the species under study. In the subgranular zone of the murine adult hippocampus, proliferation of immature neurons is increased at the middle of the dark phase (*Zeitgeber* Time 18: ZT18) coincident with the maximum amplitude of melatonin secretion. Neuronal apoptosis has an anti-phase relationship with proliferation, having a peak at the middle of the light phase (ZT6) when melatonin levels are low. These rhythmic patterns were present only in mice with functional melatonin MT₁ and MT₂ receptors (Fredrich *et al.*, 2017). Interestingly, in zebrafish, which is a diurnal-active vertebrate, and in mice who are nocturnal-active, the different stages of the cell cycle in neurogenic niches display a circadian pattern that reaches its maximum levels during the dark phase (Bouchard-Cannon *et al.*, 2013; Akle *et al.*, 2017). These patterns correlate with the expression of clock genes *Clock1* and *Per1* in zebrafish (Akle *et al.*, 2017), and with *Per2* and *Bmal1* in mice (Bouchard-Cannon *et al.*, 2013). It is well known that cell proliferation is under the control of clock genes in most mammalian cells, and melatonin can modulate clock proteins at the level of gene expression (Imbesi *et al.*, 2009). Moreover, melatonin might regulate the half-life of clock proteins by timing their degradation in the proteasome.

Neuroplastic changes in dendrites also display a circadian rhythm. A temporal analysis of hippocampal dendritic structure in Siberian hamsters revealed photoperiod length-dependent changes that occur during the dark phase of the cycle and were more significant in basilar dendrites of CA1 pyramidal neurons. During short days (8 h L : 16 h D), the number of branch points significantly increases, indicating a more complex dendritic tree, while during long days (16 h L : 8 h D), there is an increase in dendrite length. Exogenous melatonin administration in the late hours of the light phase induces the nocturnal dendritic morphology in CA1 neurons within 4 h. These changes occur together with an increase in the expression of clock genes *Per1* and *Bmal1* in the hippocampus (Ikeno and Nelson, 2015). Either in short or long photoperiod schemes, the duration of endogenous melatonin secretion peak would be proportional to the length of the dark phase, providing seasonal information to the organism. Whether the differential effects observed in dendrite morphology are modulated by a shorter or longer exposure to endogenous melatonin would be very interesting to find out.

Circadian rhythms in synaptic plasticity have been studied by both structural and electrophysiological approaches. The former showed a circadian pattern reaching a maximum number or size of hippocampal dendritic spines during the dark phase in mice (Ikeno *et al.*, 2015). However, studies in Siberian hamsters indicate a decrease in dendritic spine density during the dark phase in the dentate gyrus (Ikeno and Nelson, 2015). Electrophysiological studies have shown that hippocampal LTP, which is indicative of synaptic strength, was greater in magnitude and had an increased stability in slices obtained from mice killed during the dark phase (Chaudhury *et al.*, 2005). This pattern persisted even in constant darkness conditions or in slices obtained at daytime and LTP-induction assessed at night-time, suggesting an endogenous rhythm in synaptic plasticity that could be maintained *ex vivo* in a brain slice. Melatonin exerts an inhibitory effect on hippocampal induced-LTP, over a wide range of concentrations (1 nM to 100 µM) (Wang *et al.*, 2005). It is important to mention that these experiments (i.e. hippocampal slices preparation and electrophysiological recordings) were completed during the light phase of the cycle. Thus, interpretation of results is difficult in the context of the possible role of endogenous melatonin in modulating the circadian synaptic plasticity. In summary, the data suggest that hippocampal neuroplasticity is under the influence of the light/dark cycle and melatonin modulation.

Chronodisruption

The light/dark cycle is the most predictable of the environmental cycles and constitutes the strongest *Zeitgeber* indicating external time for synchronization of circadian rhythms. The lifestyle of modern humans demands that activity is no longer restricted to the natural cycle of illumination. Instead, most of the world's populations nowadays are exposed to non-natural conditions of light at night (LAN), disrupting circadian rhythms including the nocturnal synthesis and secretion of melatonin (Navara and Nelson, 2007). Other important *Zeitgeber* systems, such as food intake and social activity, are also affected in our 24/7 society. Detrimental consequences for human health associated with misalignment or disruption between external time cues and endogenous rhythms have become a matter of scientific concern in recent years. In this sense, the term *chronodisruption* was coined to define 'a relevant disturbance of the circadian organization of physiology, endocrinology, metabolism and behavior' (Erren and Reiter, 2013).

Chronodisruption has been associated with an increased number of pathologies including mood disorders (Bedrosian and Nelson, 2017). In animal paradigms of chronodisruption, that is, exposure to constant light (LL) or dim-LAN, both behaviour and hippocampal neuroplasticity are altered. In mice, LL exposure leads to impaired hippocampal neurogenesis and defective cognitive performance (Fujioka *et al.*, 2011), as well as an increase in behavioural despair in the FST (Fonken *et al.*, 2009). Rats subjected to chronic LL-exposure displayed both anhedonic- and anxiety-like behaviours and altered patterns of cellular activation in the

SCN (Tapia-Osorio *et al.*, 2013). A similar effect was found in dim-LAN-exposed mice (Fonken and Nelson, 2013) and hamsters that presented increased immobility time in the FST and diminished preference to sucrose solution. These altered behaviours correlated with reduced dendritic spine density in hippocampal CA1 neurons and with decreased *BDNF* gene expression in the hippocampus, relative to animals exposed to a standard light/dark cycle. Interestingly, the biochemical, morphological and behavioural alterations caused by a chronic 4-week dim-LAN exposure were reversible after a 2-week exposure to the regular light/dark cycle (Bedrosian *et al.*, 2013). Similar alterations induced by dim-LAN exposure have been observed in diurnal-active rodent species.

Increased helplessness, behavioural despair and anxiety-like behaviour were observed after knocking down the expression of clock genes at the SCN in mice (Landgraf *et al.*, 2016). Also, it has been recognized that when the SCN is affected, the rhythm of melatonin release is perturbed (Bonmati-Carrion *et al.*, 2014), which might imply impairment of the oscillatory functions modulated by them. In this regard, dysfunction in hippocampal glutamate signalling and in brain plasticity mechanisms might be produced in the offspring as a consequence of gestational disruption of circadian rhythms by constant illumination.

Together, the evidence suggests that the light/dark cycle and melatonin are two important factors that influence neuroplastic changes in the hippocampus and mood (Figure 2). The increased number of nocturnal workers and

the use of electronic devices lead to inappropriate exposure to light during the night with detrimental effects in health. Therefore, it is important to generate public health strategies for light hygiene, that is, a 'circadian healthy light exposure' (Bonmati-Carrion *et al.*, 2014). From our point of view, a thorough re-evaluation of the potential of melatonin chronotherapy as an alternative for depressive patients, given alone or in combination with current antidepressant treatments, is worthwhile and needs to be undertaken.

In summary, neuroplasticity is an important process that follows a circadian rhythm for maintaining appropriate mental health. The hippocampus is one of the most affected structures in mood disorders and an important target of the modulatory effects of melatonin. Administration of exogenous melatonin prevents neuronal damage and may stabilize circadian rhythms of neuroplasticity. The preclinical evidence indicates that melatonin augmented the neuroplastic changes in the hippocampus. However, it is necessary to demonstrate its effectiveness in the treatment of depressive patients to obtain translational evidence. Therefore, MRI studies in healthy subjects and in patients with mood disorders are necessary to know if reduced densities and sizes of neurons and reduced hippocampal volumes in depressive patients could be reversed by melatonin administration. Also, it is necessary to know by clinical studies if melatonin co-administered with conventional antidepressant treatments causes the reversal of symptoms and of the abnormalities in the hippocampal volume.

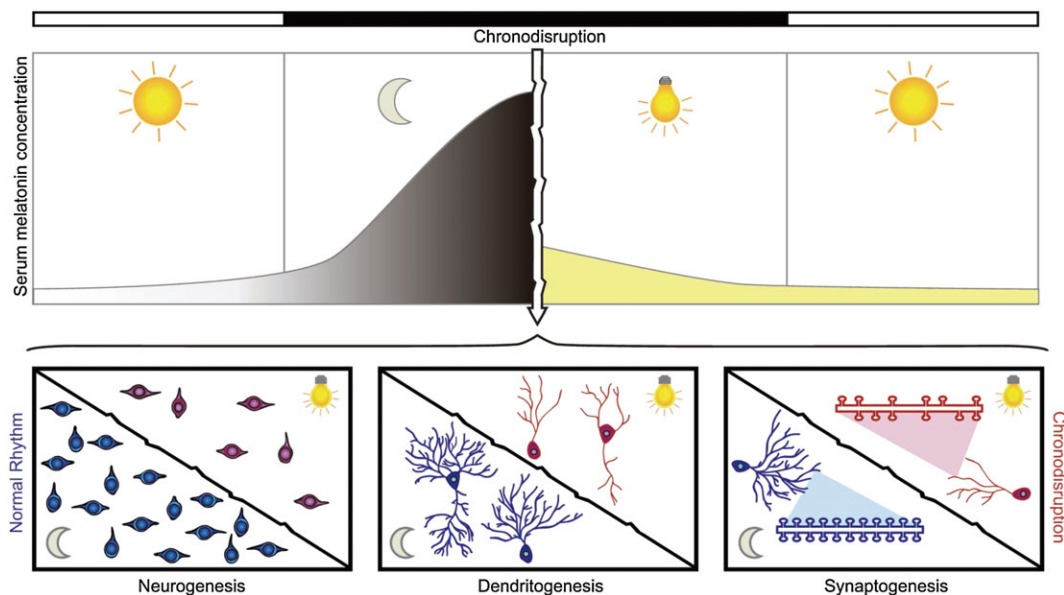


Figure 2

Chronodisruption in neuroplasticity processes related to mood disorders. Our modern society is subjected to artificial light at night (LAN) among other conditions that cause an overall disruption of circadian rhythms. The horizontal bars indicate the phases of the environmental light/dark cycle (light: white bar; dark: black bar). The upper panel represents the serum melatonin concentration, which would reach its higher amplitude during the dark phase. The white arrow indicates chronodisruption by exposure to LAN that inhibits melatonin synthesis and secretion and thus the rhythm of its circulating levels is blunted. In preclinical studies, this condition causes detrimental effects in neuroplasticity processes such as neurogenesis, dendritogenesis and synaptogenesis (represented in lower panels), which have been related to the aetiology of mood disorders and their increasing prevalence in the last decades.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander *et al.*, 2017a,b).

Acknowledgements

This study was supported by Consejo Nacional de Ciencia y Tecnología grant 178075 to G.B.-K. and grant 252935 to C.T.

Conflicts of interest

The authors declare no conflicts of interest.

References

- Akle V, Stankiewicz AJ, Kharchenko V, Yu L, Kharchenko PV, Zhdanova IV (2017). Circadian kinetics of cell cycle progression in adult neurogenic niches of a diurnal vertebrate. *J Neurosci* 37: 1900–1909.
- Alexander SPH, Christopoulos A, Davenport AP, Kelly E, Marrion NV, Peters JA *et al.* (2017a). The Concise Guide to PHARMACOLOGY 2017/18: G protein-coupled receptors. *Br J Pharmacol* 174: S17–S129.
- Alexander SPH, Kelly E, Marrion NV, Peters JA, Faccenda E, Harding SD *et al.* (2017b). The Concise Guide to PHARMACOLOGY 2017/18: Transporters. *Br J Pharmacol* 174: S360–S446.
- Anderson G (2017). Linking the biological underpinnings of depression: role of mitochondria interactions with melatonin, inflammation, sirtuins, tryptophan catabolites, DNA repair and oxidative and nitrosative stress, with consequences for classification and cognition. *Prog Neuropsychopharmacol Biol Psychiatry* 80: 255–266.
- Bavithra S, Sugantha Priya E, Selvakumar K, Krishnamoorthy G, Arunakaran J (2015). Effect of melatonin on glutamate: BDNF signaling in the cerebral cortex of polychlorinated biphenyls (PCBs)-exposed adult male rats. *Neurochem Res* 40: 1858–1869.
- Beck-Friis J, Kjellman BF, Aperia B, Undén F, von Rosen D, Liunggren JG *et al.* (1985). Serum melatonin in relation to clinical variables in patients with major depressive disorder and a hypothesis of a low melatonin syndrome. *Acta Psychiatr Scand* 71: 319–330.
- Bedrosian TA, Nelson RJ (2017). Timing of light exposure affects mood and brain circuits. *Transl Psychiatry* 7: e1017.
- Bedrosian TA, Weil ZM, Nelson RJ (2013). Chronic dim light at night provokes reversible depression-like phenotype: possible role for TNF. *Mol Psychiatry* 18: 930–936.
- Bonmati-Carrion MA, Arguelles-Prieto R, Martinez-Madrid MJ, Reiter R, Hardeband R, Rol MA *et al.* (2014). Protecting the melatonin rhythm through circadian healthy light exposure. *Int J Mol Sci* 15: 23448–23500.
- Bouchard-Cannon P, Mendoza-Viveros L, Yuen A, Kaern M, Cheng HY (2013). The circadian molecular clock regulates adult hippocampal neurogenesis by controlling the timing of cell-cycle entry and exit. *Cell Rep* 5: 961–973.
- Castren E, Rantamaki T (2010). The role of BDNF and its receptors in depression and antidepressant drug action: reactivation of developmental plasticity. *Dev Neurobiol* 70: 289–297.
- Chaudhury D, Wang LM, Colwell CS (2005). Circadian regulation of hippocampal long-term potentiation. *J Biol Rhythms* 20: 225–236.
- Chenu F, El Mansari M, Blier P (2013). Electrophysiological effects of repeated administration of agomelatine on the dopamine, norepinephrine, and serotonin systems in the rat brain. *Neuropsychopharmacology* 38: 275–284.
- De Butte M, Pappas BA (2007). Pinealectomy causes hippocampal CA1 and CA3 cell loss: reversal by melatonin supplementation. *Neurobiol Aging* 28: 306–313.
- De Crescenzo F, Lennox A, Gibson JC, Cordey JH, Stockton S, Cowen PJ *et al.* (2017). Melatonin as a treatment for mood disorders: a systematic review. *Acta Psychiatr Scand* 136: 549–558.
- Demirkan A, Lahti J, Direk N, Viktorin A, Lunetta KL, Terracciano A *et al.* (2016). Somatic, positive and negative domains of the Center for Epidemiological Studies Depression (CES-D) scale: a meta-analysis of genome-wide association studies. *Psychol Med* 46: 1613–1623.
- Detanico BC, Piato AL, Freitas JJ, Lhullier FL, Hidalgo MP, Caumo W *et al.* (2009). Antidepressant-like effects of melatonin in the mouse chronic mild stress model. *Eur J Pharmacol* 607: 121–125.
- Domínguez-Alonso A, Ramírez-Rodríguez G, Benítez-King G (2012). Melatonin increases dendritogenesis in the hilus of hippocampal organotypic cultures. *J Pineal Res* 52: 427–436.
- Domínguez-Alonso A, Valdés-Tovar M, Solís-Chagoyán H, Benítez-King G (2015). Melatonin stimulates dendrite formation and complexity in the hilar zone of the rat hippocampus: participation of the Ca⁺⁺/Calmodulin complex. *Int J Mol Sci* 16: 1907–1927.
- Drevets WC, Price JL, Furey ML (2008). Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Funct* 213: 93–118.
- Dubocovich ML, Hudson RL, Sumaya IC, Masana MI, Manna E (2005). Effect of MT1 melatonin receptor deletion on melatonin-mediated phase shift of circadian rhythms in the C57BL/6 mouse. *J Pineal Res* 39: 113–120.
- Emens JS, Burgess HJ (2015). Effect of light and melatonin and other melatonin receptor agonists on human circadian physiology. *Sleep Med Clin* 10: 435–453.
- Erren TC, Reiter RJ (2013). Revisiting chronodisruption: when the physiological nexus between internal and external times splits in humans. *Naturwissenschaften* 100: 291–298.
- Etain B, Milhiet V, Belliver F, Leboyer M (2011). Genetics of circadian rhythms and mood spectrum disorders. *Eur Neuropsychopharmacol* 21 (Suppl 4): S676–S682.
- Evely KM, Hudson RL, Dubocovich ML, Haj-Dahmane S (2016). Melatonin receptor activation increases glutamatergic synaptic transmission in the rat medial lateral habenula. *Synapse* 70: 181–186.
- Fonken LK, Finy MS, Walton JC, Weil ZM, Workman JL, Ross J *et al.* (2009). Influence of light at night on murine anxiety- and depressive-like responses. *Behav Brain Res* 205: 349–354.

- Fonken LK, Nelson RJ (2013). Dim light at night increases depressive-like responses in male C3H/HeN^{hsd} mice. *Behav Brain Res* 243: 74–78.
- Fredrich M, Hampel M, Seidel K, Christ E, Korf HW (2017). Impact of melatonin receptor-signaling on Zeitgeber time-dependent changes in cell proliferation and apoptosis in the adult murine hippocampus. *Hippocampus* 27: 495–506.
- Fujioka A, Fujioka T, Tsuruta R, Izumi T, Kasaoka S, Maekawa T (2011). Effects of a constant light environment on hippocampal neurogenesis and memory in mice. *Neurosci Lett* 488: 41–44.
- Garzón C, Guerrero JM, Aramburu O, Guzmán T (2009). Effect of melatonin administration on sleep, behavioral disorders and hypnotic drug discontinuation in the elderly: a randomized, double-blind, placebo-controlled study. *Aging Clin Exp Res* 21: 38–42.
- Golden RN, Gaynes BN, Ekstrom RD, Hamer RM, Jacobsen FM, Suppes T *et al.* (2005). The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry* 162: 656–662.
- Hardeland R (2013). Chronobiology of melatonin beyond the feedback to the suprachiasmatic nucleus—consequences to melatonin dysfunction. *Int J Mol Sci* 14: 5817–5841.
- Harding SD, Sharman JL, Faccenda E, Southan C, Pawson AJ, Ireland S *et al.* (2018). The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. *Nucl Acids Res* 46: D1091–D1106.
- Hashimoto K (2009). Emerging role of glutamate in the pathophysiology of major depressive disorder. *Brain Res Rev* 61: 105–123.
- Hillhouse TM, Porter JH (2015). A brief history of the development of antidepressant drugs: from monoamines to glutamate. *Exp Clin Psychopharmacol* 23: 1–21.
- Hunt AE, Al-Ghoul WM, Gillette MU, Dubocovich ML (2001). Activation of MT(2) melatonin receptors in rat suprachiasmatic nucleus phase advances the circadian clock. *Am J Physiol Cell Physiol* 280: C110–C118.
- Ikeda M, Hojo Y, Komatsuzaki Y, Okamoto M, Kato A, Takeda T *et al.* (2015). Hippocampal spine changes across the sleep-wake cycle: corticosterone and kinases. *J Endocrinol* 226: M13–M27.
- Ikeno T, Nelson RJ (2015). Acute melatonin treatment alters dendritic morphology and circadian clock gene expression in the hippocampus of Siberian hamsters. *Hippocampus* 25: 142–148.
- Imbesi M, Arslan AD, Yildiz S, Sharma R, Gavin D, Tun N *et al.* (2009). The melatonin receptor MT1 is required for the differential regulatory actions of melatonin on neuronal 'clock' gene expression in striatal neurons in vitro. *J Pineal Res* 46: 87–94.
- Kandalepas PC, Mitchell JW, Gillette MU (2016). Melatonin signal transduction pathways require E-box-mediated transcription of *Per1* and *Per2* to reset the SCN clock at dusk. *PLoS One* 11: e0157824.
- Kendler KS, Karkowski LM, Prescott CA (1999). Causal relationship between stressful life events and the onset of major depression. *Am J Psychiatry* 156: 837–841.
- Landgraf D, Long JE, Proulx CD, Barandas R, Malinow R, Welsh DK (2016). Genetic disruption of circadian rhythms in the suprachiasmatic nucleus causes helplessness, behavioral despair, and anxiety-like behavior in mice. *Biol Psychiatry* 80: 827–835.
- Landgraf D, McCarthy MJ, Welsh DK (2014). Circadian clock and stress interactions in the molecular biology of psychiatric disorders. *Curr Psychiatry Rep* 16: 483.
- Liu C, Weaver DR, Jin X, Shearman LP, Pieschl RL, Gribkoff VK *et al.* (1997). Molecular dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock. *Neuron* 19: 91–102.
- Liu D, Wei N, Man HY, Lu Y, Zhu LQ, Wang JZ (2015). The MT2 receptor stimulates axonogenesis and enhances synaptic transmission by activating Akt signaling. *Cell Death Differ* 22: 583–596.
- Liu J, Clough SJ, Dubocovich ML (2017). Role of the MT1 and MT2 melatonin receptors in mediating depressive- and anxiety-like behaviors in C3H/HeN mice. *Genes Brain Behav* 16: 546–553.
- Liu J, Somera-Molina KC, Hudson RL, Dubocovich ML (2013). Melatonin potentiates running wheel-induced neurogenesis in the dentate gyrus of adult C3H/HeN mice hippocampus. *J Pineal Res* 54: 222–231.
- Madsen MT, Isbrand A, Andersen UO, Andersen LJ, Taskiran M, Simonsen E *et al.* (2017). The effect of Melatonin on Depressive symptoms, Anxiety, Circadian and Sleep disturbances in patients after acute coronary syndrome (MEDACIS): study protocol for a randomized controlled trial. *Trials* 18: 81.
- Mantovani M, Pertile R, Calixto JB, Santos AR, Rodrigues AL (2003). Melatonin exerts an antidepressant-like effect in the tail suspension test in mice: evidence for involvement of N-methyl-D-aspartate receptors and the L-arginine-nitric oxide pathway. *Neurosci Lett* 343: 1–4.
- Micale V, Arezzi A, Rampello L, Drago F (2006). Melatonin affects the immobility time of rats in the forced swim test: the role of serotonin neurotransmission. *Eur Neuropsychopharmacol* 16: 538–545.
- Navara KJ, Nelson RJ (2007). The dark side of light at night: physiological, epidemiological, and ecological consequences. *J Pineal Res* 43: 215–224.
- Overstreet DH, Pucilowski O, Retton MC, Delagrangé P, Guardiola-Lemaitre B (1998). Effects of melatonin receptor ligands on swim test immobility. *Neuroreport* 9: 249–253.
- Pascual R, Bustamante C (2010). Melatonin promotes distal dendritic ramifications in layer II/III cortical pyramidal cells of rats exposed to toluene vapors. *Brain Res* 1355: 214–220.
- Raghavendra V, Kaur G, Kulkarni SK (2000). Anti-depressant action of melatonin in chronic forced swimming-induced behavioral despair in mice, role of peripheral benzodiazepine receptor modulation. *Eur Neuropsychopharmacol* 10: 473–481.
- Ramirez-Rodriguez G, Klempin F, Babu H, Benítez-King G, Kempermann G (2009). Melatonin modulates cell survival of new neurons in the hippocampus of adult mice. *Neuropsychopharmacology* 34: 2180–2191.
- Rennie K, De Butte M, Pappas BA (2009). Melatonin promotes neurogenesis in dentate gyrus in the pinealectomized rat. *J Pineal Res* 47: 313–317.
- Serfaty MA, Osborne D, Buszewicz MJ, Blizard R, Raven PW (2010). A randomized double-blind placebo-controlled trial of treatment as usual plus exogenous slow-release melatonin (6 mg) or placebo for sleep disturbance and depressed mood. *Int Clin Psychopharmacol* 25: 132–142.
- Souète E, Salvati E, Belugou JL, Pringuey D, Candito M, Krebs B *et al.* (1989). Circadian rhythms in depression and recovery: evidence for blunted amplitude as the main chronobiological abnormality. *Psychiatry Res* 28: 263–278.

Sumaya IC, Masana MI, Dubocovich ML (2005). The antidepressant-like effect of the melatonin receptor ligand luzindole in mice during forced swimming requires expression of MT2 but not MT1 melatonin receptors. *J Pineal Res* 39: 170–177.

Tapia-Osorio A, Salgado-Delgado R, Angeles-Castellanos M, Escobar C (2013). Disruption of circadian rhythms due to chronic constant light leads to depressive and anxiety-like behaviors in the rat. *Behav Brain Res* 252: 1–9.

Treadway MT, Waskom ML, Dillon DG, Holmes AJ, Park MT, Chakravarty MM *et al.* (2015). Illness progression, recent stress, and morphometry of hippocampal subfields and medial prefrontal cortex in major depression. *Biol Psychiatry* 77: 285–294.

Wang LM, Suthana NA, Chaudhury D, Weaver DR, Colwell CS (2005). Melatonin inhibits hippocampal long-term potentiation. *Eur J Neurosci* 22: 2231–2237.

Weil ZM, Hotchkiss AK, Gatien ML, Pieke-Dahl S, Nelson RJ (2006). Melatonin receptor (MT1) knockout mice display depression-like behaviors and deficits in sensorimotor gating. *Brain Res Bull* 68: 425–429.

Zhang L, Zhang HQ, Liang XY, Zhang HF, Zhang T, Liu FE (2013). Melatonin ameliorates cognitive impairment induced by sleep deprivation in rats: role of oxidative stress, BDNF and CaMKII. *Behav Brain Res* 256: 72–81.