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REVIEW ARTICLE

Dysregulation of Circadian Rhythms in Autism Spectrum Disorders

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Abstract: ***Background*:** The alterations in neurological and neuroendocrine functions observed in the autism spectrum disorder (ASD) involves environmentally dependent dysregulation of neurodevelopment, in interaction with multiple coding gene defects. Disturbed sleep-wake patterns, as well as abnormal melatonin and glucocorticoid secretion, show the relevance of an underlying impairment of the circadian timing system to the behavioral phenotype of ASD. Thus, understanding the mechanisms involved in the circadian dysregulation in ASD could help to identify early biomarkers to improve the diagnosis and therapeutics as well as providing a significant impact on the lifelong prognosis.

***Objective*:** In this review, we discuss the organization of the circadian timing system and explore the connection between neuroanatomic, molecular, and neuroendocrine responses of ASD and its clinical manifestations. Here we propose interconnections between circadian dysregulation, inflammatory baseline and behavioral changes in ASD. Taking into account, the high relevancy of melatonin in orchestrating both circadian timing and the maintenance of physiological immune quiescence, we raise the hypothesis that melatonin or analogs should be considered as a pharmacological approach to suppress inflammation and circadian misalignment in ASD patients.

***Strategy*:** This review provides a comprehensive update on the state-of-art of studies related to inflammatory states and ASD with a special focus on the relationship with melatonin and clock genes. The hypothesis raised above was analyzed according to the published data.

***Conclusion*:** Current evidence supports the existence of associations between ASD to circadian dysregulation, behavior problems, increased inflammatory levels of cytokines, sleep disorders, as well as reduced circadian neuroendocrine responses. Indeed, major effects may be related to a low melatonin rhythm. We propose that maintaining the proper rhythm of the circadian timing system may be helpful to improve the health and to cope with several behavioral changes observed in ASD subjects.

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1. INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder involving gene polymorphisms, intra-uterine and post-natal environment, autoimmune, and inflammatory factors. The diagnosis of ASD is based on behavioral changes, rather than its etiology, and may be disclosed in non-dimorphic patients, as observed in the majority of the cases, while sometimes may possess clinical manifestations as observed in some genetic syndromes [1, 2]. Neither genetic factors nor the environmental components have been extensively characterized to allow a proper diagnosis and treatment of non-syndromic ASD. Although its etiology is not fully understood, changes in brain development impose maladaptation of several structures and functions that are reflected in atypical behavioral alterations [3-5]. The prevalence of ASD, more common in boys rather than girls, has increased significantly throughout recent decades [6]. As a major structural problem, the brain alterations reveal a continuum of behavioral features characterized by persistent abnormal reciprocal social interactions, stereotyped and restricted patterns of behavior, interests, or activities, atypical sensory reactivity and profound impairment in verbal and nonverbal communication [7].

The etiology of ASD is complex and no major contributor was fully determined in the majority of the cases [8]. In some cases, there are changes in the expression of genes associated with the development and function of the central nervous system, as observed for single nucleotide polymorphisms (SNPs) of genes involved in neural development and synaptic activities [9]. The intrauterine environment is considered a relevant factor to contribute to ASD etiology due to the increased production of pro-inflammatory cytokines, which can transpose the placental barrier and affect the development of the central nervous system of the fetus [10-12]. The changes in the brain structure of autism include deficits in the connections among different brain areas [13] and synapses formation [14, 15], as well as dysfunction of glial cells [15] and mutations in genes that control several aspects of the circadian oscillations of the body [16], which may include the neuroendocrine responses of this system, as for the rhythm of melatonin synthesis, which *per se* is an important hallmark for the regulation of endogenous rhythmic functions [17].

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The disruption of the sleep-wake cycle is also a very common feature in the ASD phenotype. Indeed, 40–93% of ASD subjects may present alterations of sleep [18-23] and represents a circadian disturbance that can promote additional neurobehavioral dysfunctions as negatively influences cognition and behavior [20, 24-26], as well as changing endocrine responses, as melatonin and cortisol secretion [20, 27-29]. Although circadian rhythm dysregulation during brain development was suggested to be causative of ASD [18, 30,31], it must be highlighted that also healthy subjects present sleep disturbances and related behavioral problems [20, 32-34]. Besides the increased bulk of studies that have evaluated several aspects of ASD etiology, it has been remarkable the understanding of the multifactorial association between several aspects of circadian misalignment and the clinical manifestations of ASD. Here we present mechanisms involved in the disruption of circadian rhythms by covering the basic mechanism of normal organization of the circadian timing system and its close association between neuroendocrine and neurobehavioral functions. Finally, we included our current working hypothesis which suggests that at least part of the behavioral symptoms in ASD is caused by an inflammatory state linked to the disruption of melatonin production. Moreover, these mechanisms are underneath sleep and cognitive disorders typical of ASD.

2. ORGANIZATION OF THE CIRCADIAN TIMING SYSTEM

The circadian rhythm in mammals is driven by the central clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus. These important nuclei in the brain adjust the timing of several aspects of the physiology to the daily environmental lighting by perceiving the light in the retina and integration of this information to the master clock, the SCN [35]. A neuroendocrine connection between SCN and the whole body involves the early morning peak of cortisol and the nocturnal peak of melatonin. The high relevance of this system for human settings relies on the premise that the circadian timing system allows the body to anticipate and prepare for changes that occur in the natural environment, thus improving its physiological strength to orchestrate behavior and physiological functions to the oscillation of light in the environment [36, 37].

The oscillatory machinery of the SCN is based on the transcriptional feedback loops of coding genes and its proteins [35, 38]. Transcriptional feedback involves at least eleven genes [38]. Briefly, the heterodimer Bmal1: Clock rhythmically assembled by the circadian transcription of *Bmal1* (also known as *ARNT*) leads to the transcription of the repressor genes *Per1*, *Per2*, *Cry1,* and *Cry2*. The proteins translated from these genes form homo- or heterodimers that suppress Bmal1: Clock activity. Such transcription/translation rates repeat over an approximately 24-hour period (*circadian*, from the Latin, around one day) [35, 39]. The robust circadian endogenous rhythm of the SCN is transmitted to the whole body by neural and hormonal connections, synchronizing cells, tissues, and functions.

Light input to the SCN is mediated by the direct retinohypothalamic tract, which initiates in the photoreceptive ganglion cells in the retina [40]. Also, non-photic signals, including molecular changes typical of some pathologies, may influence the SCN and consequently alter the biological rhythms [41-43]. Thus, the synchrony of the SCN to light is mediated by specific cells of the retina that project to the SCN and other thalamic areas [44]. Environmental light is the major zeitgeber for the SCN, however, activity, temperature, and social interaction are relevant secondary time givers [39, 43, 45].

For the orchestration of typical circadian rhythmic behaviors, the connections from the SCN to other areas are established primarily through a relay in the hypothalamic paraventricular nucleus (PVN), an important neuroanatomic link for inducing neuroendocrine responses, with implications for biological rhythms, metabolism, immune system, autonomic nervous system and emotional behavior control [44, 46] (Fig. **1**).

Thus, SCN orchestrates many complex 'timed' internal systems, such as body temperature, endocrine functions, and blood pressure. The rhythmic clock gene expression within the SCN is translated to multiple brain regions and control mood and motivational behaviors, stress reward circuits, arousal, and sleep by interacting with the homeostatic regulation of sleep and wake patterns [47]. As master brain oscillator, it must act in synchronicity to the peripheral oscillatory system, which is well known to co-exist under a hierarchical control from the SCN. Otherwise, the conflict between the SCN-driven rhythms to peripheral oscillators can reset several physiological functions by many parallel signals [48, 49]. Thus, the circadian timing of the organism is a complex system subject to different grades of misfits.

Abnormal circadian rhythms were shown to increase the risk for, as well as the severity of ASD [14, 30]. Desynchronization of hormone secretion, thermoregulation, locomotor activity, and sleep was associated with early alterations in the development of autistic children´s brains [17, 26, 50-52].

The lack of control in the timing of brain development due to abnormalities in clock gene machinery was correlated with behavioral changes [53]. Indeed, the involvement of clock genes in ASD has been described [54]. Significant allelic association of polymorphisms in *PER1* and Neuronal PAS domain protein 2 (*NPAS2*) and ASD [16], SNPs in the coding region of Nuclear Receptor subfamily 1, group D, member 1 (*NR1D1*) a gene coding for the control of transcription of *Bmal1* gene [55] as well as mutations/SNPs in *CLOCK* and in *NR1D1* and *ARNT2* that encode proteins linked to sleep disorders were described [56]. The relationship between a mutation in clock gene machinery and circadian-related genes and sleep is also an important subject in ASD [57-59], as it was shown to result in cognitive, attentional, and psychiatric disorders [20, 60].

3. MELATONIN: JUST THE HORMONE OF DARKNESS?

The 'chemical signal of darkness', melatonin, was first discovered and isolated from the bovine pineal gland extracts in 1958 by Aaron Lerner studies of pigment aggregation in frog skin melanophores [62]. Subsequently to its discovery, melatonin's action in reproductive function was readily proposed. Later on, several researchers confirmed this indoleamine as a neuroendocrine factor secreted by the pineal gland in a variety of species under the synchrony of the environmental lighting and under the strict control of the SCN [63]. Recently, several studies demonstrated that fine-tuning the nocturnal synthesis of melatonin may also integrate external lighting to endogenous homeostasis, as the pineal gland, a circumventricular organ, also senses endogenous molecules, including glucocorticoids and inflammatory mediators, which may have consequences for health and disease [64].

The neural integration from the SCN for allowing the synthesis of melatonin by the pineal gland involves a multi-synaptic pathway that links the SCN, PVN, and the superior cervical ganglion (SCG), where sympathetic postganglionic axons emerge to the gland through the pineal stalk releasing norepinephrine at the dark phase, activating the synthesis of melatonin [65]. The PVN is an important relay for SCN-controlling melatonin synthesis as its lesion abolishes the nocturnal rise in melatonin production [66].

For the rhythmic production of cortisol, the SCN acts through two pathways: the first, by a neuroendocrine response, which consists of the action of the PVN on the adenohypophysis inducing the secretion of adrenocorticotropic hormone (ACTH) that *via* systemic circulation acts on the adrenal gland cortex. The other pathway occurs *via* the neural pathway, where PVN stimulatory neurotransmission, *via* the spinal cord mid-spinal column, induces the synthesis of cortisol [67].

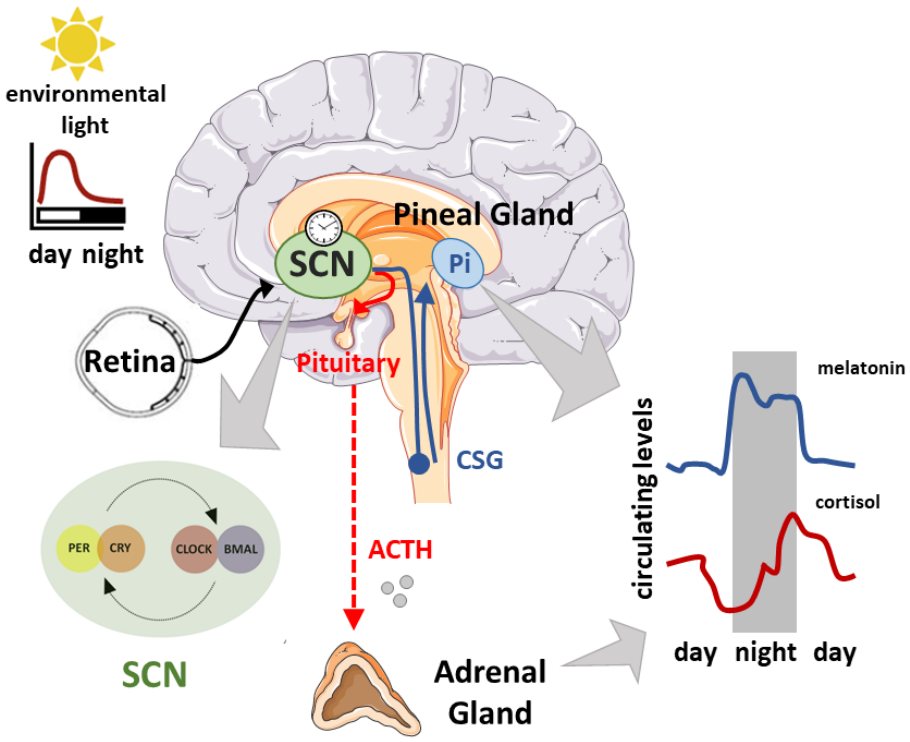

Fig. (1). Organization of the circadian timing system: cyclic variation in the environmental light (day and night) are sensed by melanopsin-expressing photoreceptors in the retina (retinal ganglion cells) which project this information through neurotransmission to the suprachiasmatic nuclei (SCN) of the hypothalamus, *via* retinohypothalamic tract, thus synchronizing the transcription and activity of the clock gene machinery. From the SCN, major control of neuroendocrine rhythms is due to projections to the paraventricular nuclei (PVN) of the hypothalamus, which regulates the synthesis of cortisol and melatonin in a phase-dependent manner. For the synthesis of cortisol, major effects are due to the control of the PVN on the adenohypophysis inducing the secretion of adrenocorticotropic hormone (ACTH), that *via* systemic circulation acts on the adrenal gland cortex (red lines). The other pathway occurs *via* the neural pathway, where PVN stimulatory neurotransmission, *via* the spinal cord mid-spinal column, induces the synthesis of cortisol in the adrenal gland (not shown in the schematic representation). The neural integration from the SCN for allowing the pineal gland (Pi) synthesis of melatonin involves a multi-synaptic pathway that links the SCN, paraventricular nucleus (PVN), and the superior cervical ganglion (SCG), where postganglionic axons emerge to the gland through the pineal stalk and release norepinephrine directly into pineal gland at the dark phase. In humans, the peak of cortisol in the circulation occurs in the transition between dark to the light phase, thus informing the onset of activity, whereas the peak of melatonin occurs only in the presence of darkness and plays major effects in the orchestration of nocturnal rhythms of humans. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

It is interesting to note that in most mammals, the rhythmic production of these hormones occurs in specific phases, which generates patterns in the production and action of these hormones. In general, the increase in glucocorticoid synthesis and secretion precedes the activity phase of the species, while melatonin production occurs systematically during the dark phase in most species. Also, to promote proper timing of the organism to the environment, cross-communication in the actions of glucocorticoids and melatonin may allow responses that suit the organism's rhythmic events. Under physiological conditions, the reciprocal synchronization between adrenal and pineal gland activity in rats is of great relevance for the regulation of different physiological responses, which demonstrates the existence of a cross-communication between the rhythmic activities of these two glands [68]. In species that exhibit diurnal activity, such as humans, an increase in the cortisol plasma content is observed in the morning, maintaining melatonin production at night. Thus, the synchronization of the organism's rhythmic patterns to a single synchronizer (SCN) orchestrates the proper functioning of structures and tissues that allow their respective activities in a time-regulated manner.

During the light phase of the day, the SCN oscillation inhibits PVN-to-SCG neural activity by GABAergic neurotransmission. At night, glutamatergic-excitatory neurotransmission activates PVN neurons. The dorsal and lateral neurons of PVN are the main projections to reach the neurons in the SCG [69]. Thus, major deficits in intra-uterine development of these brain areas may impact the nocturnal synthesis of melatonin. The dense pineal innervation by the sympathetic postganglionic axons triggers the nocturnal release of noradrenaline [70] and ATP co-transmission [71]. Many neurotransmitters originated from other brain areas may also contribute to the regulation of melatonin synthesis [72]. However, the orchestration of noradrenaline release is timely linked to the nocturnal rise of melatonin production by the catecholamine action on β1-adrenoceptors, which are densely present in pinealocytes, the melatonin-synthesizing cells [73] (Fig. **1**).

Activation of β1-adrenoceptors in pinealocytes is translated into the activation of stimulatory G-coupled protein and formation of cyclic adenosine monophosphate (cAMP), which activates the cAMP-dependent protein kinase (PKA) that plays two major roles: firstly, it phosphorylates cAMP response element-binding protein (CREB) which binds to responsive elements in the promoter of the aralkylamine N-acetyltransferase gene (*Aanat*), starting its transcription [74, 75]. After translation, AANAT is phosphorylated by PKA, allowing its interaction to chaperone 14-3-3, and activity. *In vitro* studies have shown that the activation of α1-adrenoceptors [66] and purinergic P2Y1 receptors by ATP [71, 76] increases Ca2+-dependent protein kinase C (PKC) activation, potentiating melatonin formation [77, 78].

The nocturnal synthesis of melatonin relies on active intake of the essential amino acid tryptophan from circulation [79], which is actively hydroxylated by tryptophan hydroxylase 1 (TPH1) [80] and decarboxylated by the enzyme aromatic amino acid decarboxylase to serotonin (5-hydroxytryptamine, 5-HT) formation [81]. High levels of serotonin are constitutively produced in the pineal gland

along 24 hours [82]. However, the nocturnal activation of PKA and phosphorylation of AANAT start the conversion of 5-HT into the penultimate indoleamine in melatonin formation, N-acetylserotonin (NAS), which is methylated by the enzyme acetylserotonin O-methyltransferase (ASMT) to produce melatonin (N-acetyl-5-methoxytryptamine). Melatonin signals darkness in both diurnal and nocturnal animals. In rats, nocturnal *Aanat* expression as well as its protein activity, increase 100-150 times compared to daytime levels [66, 83]. In humans, ungulates, and rodents that display diurnal activity, this enzyme shows minor changes in gene expression but has increased nocturnal activity due to β1-adrenoceptor-induced PKA activation [84].

Melatonin is a highly amphiphilic molecule that acts in G-coupled protein receptors and subcellular compartments and is released at night into the cerebrospinal fluid (CSF), *via* the pineal recess, and bloodstream. Melatonin control over several target tissues ultimately adjusts their biological rhythms [85, 86, 87]. Besides, melatonin also regulates several cellular activities, including reduction of oxidative stress [88, 89], modulation of Ca2+-calmodulin interaction [90], and inhibition of transcription factors, such as nuclear factor kappa B (NF-κB) [91].

Melatonin, the pineal hormone, is also synthesized in extra-pineal sites [92], such as the retina [93], gastrointestinal tract [94], skin [95], immune cells [96-98], and other areas of the brain [99,100]. The synthesis of melatonin by immune-competent cells is positively mediated by NF-κB [64]. The dual effect of NF-κB in pinealocytes and monocytes/macrophages and dendritic cells is dependent on the NF-κB dimer that is translocated to the nucleus. Thus, melatonin is not only the hormone of darkness but also a mediator of defense responses. The classical hormonal effect depends on the daily rhythm mediated by pinealocyte synthesis, which is controlled by the SCN, and, therefore, the environmental lighting, whereas, the synthesis of melatonin by immune-competent cells relies on the activation of the NF-κB pathway [64].

The importance of inflammation in disturbances of brain function, including ASD gains remarkable relevance, as chronic lower-grade inflammation is underneath many neurological disturbances, including ASD [101]. Descriptions of anti-inflammatory effects of melatonin due to the ability of the molecule to donate electrons or to reduction in pro-inflammatory mediators, or induction of the anti-inflammatory hormones and cytokines are well-described in the literature [64, 97, 102]. The melatonin anti-inflammatory effects include downregulation of cyclooxygenase-2 and proinflammatory cytokines, inhibition of toll-like receptor-4 and NF-κB activation, upregulation of anti-inflammatory cytokines and antioxidant effects [64, 102-104]. Melatonin also impairs the migration of leukocytes from the blood to tissue, restraining the arrival of neutrophils [105], Despite most of the studies, anti-inflammatory effects, in some situations melatonin lead to pro-inflammatory responses. This dual effect might be obtained in the same cell model, depending on the basal state of the cells. In cultured rat cerebellar cells, the effect of melatonin varies according to a previous activation of the NF-κB pathway. In the non-activated state, melatonin leads to cell death, while in the presence of a pro-inflammatory stimulus, there is a protection of the cells. Melatonin may determine the activation of inhibition of inducible nitric oxide synthase [106]. In summary, melatonin modulates the immunological responses in healthy and pathogenic states [64, 97, 102, 103, 107-109].

A question that is still open refers to the putative physiological role of melatonin synthesized by the immune-competent cells. Overall, it is considered that the effects of extra-pineal synthesis of melatonin, remarkably not related to the orchestration of body rhythms, may also be protective of the regular function of the physiological areas of the brain. Indeed, we have a major contribution to the understanding that inflammatory signals, which block the circadian translation of melatonin production of melatonin in the pineal gland, may also protect brain areas to lipopolysaccharide (LPS)-induced neuroinflammation [100]. Importantly, in the experimental design, the cortex, hippocampus and cerebellum glial cells showed an increase in the AANAT expression, the penultimate enzyme for melatonin synthesis. This data suggests that in certain circumstances, melatonin, or even its precursor, NAS, may protect the brain for neuronal death or injury occurring along with pre-natal or postnatal neurodevelopment, or along with brain maturation. Indeed, NAS has been proposed to act on the BDNF system for regulating hippocampal neuronal network and preventing neuronal death and improving neuroanatomical connections, thus preventing loss-of-function [110].

4. SLEEP IN ASD

Humans usually spend about one-third of their lives sleeping. Although the function and implications of this process are not fully understood, it is clear that sleep problems induce several changes in the body. Sleep is paramount for the proper healthy brain development and functioning of neurocognitive functions, such as attention, memory consolidation and reasoning with a direct influence on learning, behavior, mood [20, 111-115]. Therefore, in general health, sleep is needed for the restoration of body homeostasis and influences metabolism and the immune system [116]. It is also known that prolonged sleep deprivation can represent severe physical and behavioral impairments [117, 118]. Therefore, it is relevant to highlight that misalignment of sleep may have additional consequences to several outcomes observed in ASD subjects [119].

Sleep is a complex state that presents characteristic brain electrical activity in different phases [120]. A stage of non-rapid eye movement phase (NREM) sleep called slow-wave sleep (SWS) is characterized by the presence of slow brain waves interspersed with smaller and faster waves. By the achievement in the early hours of sleep, SWS phase is concomitant with a state of relaxation and decreased tone in the peripheral muscle, reduced respiration, heart rate, and blood pressure. The individual length of SWS seems to be directly related to the need for sleep previous accumulated, which reinforces how important is the need for having a regular sleep pattern. After following deed into sleep, brain waves continue in a synchronized pattern until rapid eye movement (REM) sleep begins, which brain electrical activity and breathing become faster, it may occur an increase in heart rate, while paradoxically, blood pressure decreases and muscle tone practically disappear [121]. REM sleep plays an important role in memory consolidation, learning, as well as mood regulation [112, 113]. These phenomena reinforce the high relevance of sleep in orchestrating mood changes in ASD. Preventing sleep disturbances seems to ameliorate several aspects of behavior. Therefore, the clinical use of subjective measures of sleep, such as parent-report questionnaires and sleep diaries, are validated instruments for diagnosing ASD [122].

Physiologically, two mechanisms are responsible for sleep-wake patterns: the sleep-wake-dependent homeostatic processes and the circadian rhythms. Homeostatic pressure to initiate and maintain sleep may gradually build-up accordingly wakefulness [123, 124]. In addition to the homeostatic issue, determination of the sleep/wake cycle periodicity is characterized by the circadian timing system, even in the absence of environmental cues [124]. The harmony between homeostatic processes and circadian timing system form the typical pattern of sleep and wakefulness in adults under normal conditions, consisting of approximately 16 hours of constant wakefulness during the day and 8 hours of consolidated sleep at night, although sleep needs may change along with the course of life [123, 124]. In humans, multiple sleep/wake cycles are observed during the day and nighttime until the fourth month of age, then, daytime sleep progressively decreases, and by five years of age, the biphasic sleep/wake cycle is fully established [125, 126]. The normal sleep/wake rhythms seem to be crucial for appropriate cognitive development in children. Transient or permanent sleep

disorders are among the most common medical complaints in society and have repercussions on cognitive performance [111], behavior [20], mood [127], adaptive capacity, and quality of life [113, 128].

The most striking features of sleep disorders are usually: increased latency, difficulty initiating and/or maintaining sleep, night waking, and daytime sleepiness, which can result from sleep deprivation and interfere with productivity and quality of life [129]. Sleep problems are repeatedly observed in ASD (predominantly in initiating and maintaining sleep. *i.e* sleep latency and nocturnal awakenings) [20, 130-132].

ASD children had frequently delayed development of the circadian sleep/wake cycle in the early years of life, thus, the identification of sleep disturbances could be useful in the identification of markers of vulnerability during infant's development for early ASD screening and diagnosis since sleep problems co-occur with autistic traits in early childhood [133, 134].

The symptoms are very heterogeneous, several studies revealed that more than 70% of patients with ASD had delayed development of the expected pattern of circadian sleep/wake cycle for the age. This problem is persistent since 40–93% of children with ASD show a highly significant increase in sleep latency and nocturnal awakenings [130, 132, 135-137]. Our study in ASD individuals aged from 4 to 18 years (mean 9.7 ± 4.1 years old) showed that 59% of the individuals with ASD had indicators of at least one type of sleep disorder. The sleep-breathing disorders were the most prevalent (38% of the subjects). Besides, disorders of initiating and maintaining sleep were present in 24%, sleep-wake transition disorders were present in 13%, and sleep hyperhidrosis was present in 20% of the subjects [20]. Liu *et al*. [137] studied ASD children (age 8.8 ± 4.2) and showed that 86% had at least one sleep problem almost every day, including 54% with bedtime resistance, 56% with insomnia, 53% with parasomnias, 25% with sleep-disordered breathing, 45% with morning rise problems, and 31% with daytime sleepiness. Despite to be concordant on the major sleep problems found in ASD, the available literature data show differences in the gravity and frequency of these problems probably because of differences in methodologies and population heterogeneity. Also, sleep architecture is abnormal in ASD including, in particular, the increased proportion of stage 1 sleep, increased latency and decreased quantity in REM sleep, immature organization of REM, and decreased total sleep time [23, 138].

Clock gene polymorphisms are known to be related to rhythmic disturbances and circadian phenotypic alterations of sleep. The ability of pathological conditions to alter clock gene expression in the SCN and peripheral structures has already been described [41, 49, 139]. Guissoni Campos *et al*. [41] showed that intracerebroventricular inflammation in rodents, induced by LPS, changed Per1 and Per2 expression in the SCN indicating that a neuroinflammatory condition leads to desynchronization of primary and subordinate brain oscillators, supporting the existence of the integration between the immune and the circadian system. Inasmuch, a growing body of evidence also postulates that glia cells are necessary for maintaining a proper neuronal oscillation of the cells that drives biological rhythms in the SCN [140], thus reinforcing the key role of inflammation in altering circadian rhythms. In a rodent model of social impairment, which assembles ASD features, and developed as a result of pre-natal exposition to inflammatory stimulation, we observed worsening in the performance of strength, motor coordination, and spatial memory when compared to the controls, which was associated with increased expression of IBA1 in the microglia of hippocampal areas [141].

Some circadian genes have been associated with ASD including *PER1*, *PER2*, *PER 3*, *CLOCK* and *ARNTL2* [56]. Complex interactions between clock genes polymorphism or reduced expression and other biological factors, including the volume and malfunction of pineal gland [142,143], mutations or reduced expression of ASMT genes [144-145], with consequent abnormal melatonin secretion in the pineal gland [144, 146], abnormalities in gene expression for the melatonin receptors MT1 and MT2 [147], mutation of the fragile X mental retardation (*FMR*) gene [2], psychological, family, and social/environmental factors, including using electronic devices at night and others, which can impair the quality of sleep [22].

Sleep loss can induce inflammatory response through the activation of several cellular inflammatory mediators including the interleukins IL-6, IL-1, and tumor necrosis factor (TNF) [42]; along with the increase in the glial activation [148] and oxidative stress [149].

Sleep disturbances can affect the post-natal neurodevelopment and worsen the autistic clinical manifestations, interfering with neuronal modulation, directly related to fundamental learning processes [150]. Thus, sleep problems in ASD are correlated with behavioral changes, mood instability, and deficits in neurocognitive functions [20, 61, 119].

Children with ASD and poor sleep demonstrate significantly higher daytime behavioral problems, including irritability, externalizing behavior (specifically hyperactivity and aggression), and internalizing behaviors (behaviors lashing out at the self, such as social withdrawal, anxiety depression), compared to those who present a normal sleep pattern [21, 151]. Considering the possibilities of co-occurring conditions, many studies have indicated a potential link between insufficient sleep and attention deficit hyperactivity disorder (ADHD), one of the most common co-occurring conditions observed in ASD [152]. However, sleep problem severity in ASD is similar across ADHD and no- ADHD subgroups, which highlights that sleep disturbances in ASD is not influenced by co-occurring ADHD but favors the stereotyped behaviors [151,152].

The severity of sleep problems in ASD children becomes even clearer when parents of autistic children report changes in their sleep quality, which may be related to a result of their children's sleep problems [119]. The negative consequences of sleep disturbance can, therefore, threaten the effectiveness of behavioral treatments as a result of reduced child performance and the reduced ability of parents to correctly employ learned treatment techniques and strategies [22]. Thus, the early developmental and behavioral intervention is crucial for the management of ASD, and the success of such intervention hinges, at least partially, on the improvement in the sleep quality [30].

To investigate the rest-activity rhythm of ASD individuals, the actigraphy, which measures activity patterns *via wristwatch-like* devices that contain miniature accelerometers, may be useful for monitor along with several continuous days to accurately assess sleep patterns in children [26]. The most commonly reported behaviors across studies evaluating the rhythm of sleep patterns in ASD subjects by actigraphy are delayed sleep onset, waking up during the night as well as early morning awakening [23, 26, 135] which likely represent impairments in the generation of this circadian rhythm. Besides the sleep-wake cycle, the most widely used biomarker for the study circadian dysregulation is the melatonin rhythm, the core-body temperature, and rest-activity measures. By using these measures, together with other biomarkers, we were able to detect that ASD subjects present disruption of endocrine, immune and circadian responses, mostly related to the reduction of melatonin production and increased inflammation [153].

5. MELATONIN RHYTHM IN ASD

Among circadian disruptions in ASD, the diurnal rhythm of cortisol is altered in individuals with ASD, which present elevated cortisol in the evening [154]. A growing body of evidence also indicates abnormalities in melatonin secretion and circadian

rhythmicity in ASD [17, 29, 31, 144, 155-158]. The disruption of the melatonin biosynthesis pathway was already demonstrated in patients with ASD and their relatives, which displayed elevated whole-blood serotonin [17, 158] and decreased plasma melatonin compared with control individuals [17, 29, 31, 144, 155, 157-160]. Although some of these studies have been performed on different cohorts, as well as used different methodologies, it is clear that abnormal secretion of melatonin is a frequent trait in ASD. The melatonin deficit, mainly during the dark phase, was observed in 51-100% of individuals with ASD, and consequently, the nighttime 6-sulfatoxymelatonin excretion was significantly lower in patients with ASD than in controls [17, 29, 31]. The circadian rhythm of serum melatonin levels in autistic patients also differed from controls in amplitude and mesor [156].

Although polymorphisms in the coding gene of the enzyme ASMT have been described in ASD [17, 144], the mechanism involved in preventing the nocturnal rise in melatonin secretion in ASD subjects is not fully understood. The contribution of genetic variations in the clock genes or melatonin synthesis enzymes to melatonin deficiency is presented in only a small percentage of individuals with ASD and have not notable impacts on sleep problems [161, 162].

In our recent study [153] urinary 6-sulfatoxymelatonin (aMT6s) excretion, a melatonin metabolite that directly correlates with melatonin synthesis by the pineal gland, was arrhythmic in 40% of ASD individuals, suggesting a decrease in the nocturnal synthesis of melatonin in this population. We also observed a different pattern of melatonin excretion in the other 60% of the population analyzed: some presented a daily rhythmic variation of aMT6s excretion, similar to control subjects, and others showed a clear disruption in the rhythm (*i.e.*, nocturnal decreased aMT6s excretion or increased at the daytime level compared with control subjects).

Thus, besides SNPs mutation in ASMT seems to be a useful tool for addressing a rationale for decreased melatonin levels in ASD individuals, it has become relevant to evaluate the activation of the immune-pineal axis, which was described for acute inflammatory response in challenging the activity of the pineal gland for producing melatonin at night [64, 163] and now it is considered highly relevant in the orchestration and maintenance of the quiescence of immune responses, as absence or presence of TNF levels in humans became a hallmark for reducing the levels of melatonin in acute [164] or chronic inflammatory responses [153, 165]. By evaluating TNF levels in the saliva and the aMT6s levels excreted in the urine of control and ASD individuals, our study assessed the relationship between altered melatonin synthesis and the increased levels of the inflammatory cytokine TNF, known to be one relevant cytokine involved in sleep disorders in ASD subjects (Fig. **2**). High levels of TNF have already been detected in plasma [101] and brain [166] of individuals with ASD. Under normal neurodevelopmental conditions, TNF plays a physiological role in controlling apoptosis, neurogenesis, and neuronal cell differentiation [167], which is the biological basis for the development of cognition [168]. Increased levels of TNF result in abnormalities in neural connectivity as well as deficits in the processing information and social interaction [168]. In rodent models, activation of TNF receptors in pinealocytes leads to translocation of the NF-κB p50/p50 subunit, which inhibits *Aanat* coding gene expression [169]. Our recent study confirmed that in ASD there is an inverse correlation between melatonin and TNF levels, suggesting the relevance of pineal dysfunction in ASD mediated by inflammation [153]. Several other studies have shown that the pinealocytes express immunological receptors that may recognize pathogens and other cytokines, as well as the cytokine TNF [68, 163, 169, 170]. Thus, it is plausible to hypothesize that neurodevelopment in ASD subjects may be a result of intra-uterine *milieu*, genetic polymorphisms driven by circadian clock genes, or genes involved in neuroendocrine responses, but also the activation of the immune-pineal axis, which remains off genetic changes and is a consequence of increased inflammation.

One of the premises of the activation of the immune pineal axis relies on its ability to induce the so-called, 'extra-pineal' synthesis of melatonin outside the pineal gland. It is a matter of mention that this extra-pineal synthesis of melatonin does not follow the circadian orchestration, and thus, it is not thought to be a response derived from the SCN. On the other hand, melatonin synthesized rhythmically at the retina, but not under control of the SCN, relies as a major source for allowing retinal cell arrangement and preventing light-induced retinal damage [171,172]. On the other hand, extra-pineal synthesis of melatonin, besides a beneficial signal, maybe indicates chronodisruption, but still, prevent tissue damage.

Once synthesized, the pineal-derived melatonin is immediately released into the systemic circulation to reach peripheral and central target tissues. At this level, the melatonin distributes a nocturnal/circadian message within the entire body to regulate daily and physiological rhythms through different molecular pathways. On the other hand, extra-pineal synthesis of melatonin orchestrates non-rhythmic aspects of cellular defense in the cell of production, which may include an increase in phagocytosis and cell survival [64]. Independently on the local of its synthesis, the most well-characterized pathway for melatonin transduction is the binding and activation of the membrane specific G protein-coupled melatonin receptors MT1 and MT2 [173]. Both receptors were found to present day/night differences in expression in the SCN of rats and primates, as well in other hypothalamic areas involved in the regulation of biological rhythms [174]. The identification of mutations in the genes encoding melatonin receptors was already demonstrated in ASD [175] as well as the positive effects on sleep and behavior after the administration of the melatonin receptor agonist ramelteon [176].

Considering that the rise of the endogenous melatonin concentration is often used as a marker of a particular phase of the circadian rhythm (*i.e.* nighttime), reduction in nocturnal melatonin peak leads to a dysregulation of the temporal machinery, which may be expressed by deficient sleep consolidation and difficulty in initiating or maintaining sleep. Melatonin also affects the synchronicity of clock gene expression (*Per1*, *Per2*, *Bmal1*, *Rev-erbα*, *Clock,* and *Cry1*) in both central and peripheral target tissues [177]. In addition, pinealectomy, in animal models, abolishes the rhythmic expression of *Per1* in the *pars* tuberalis [178] and results in desynchronized *Per1* and *Per2* expressions in the SCN [179]. Agomelatine, a melatonin agonist, was effective and well-tolerated for treating insomnia and regulate circadian rhythms of sleep and temperature in ASD [180]. Taken together, these studies underlined the major role of neuroendocrine responses of melatonin in the regulation of rhythms including the sleep-wake, and body temperature cycles, and more specifically for the synchronization of peripheral oscillators (*i.e.*, in the adjustment of the timing of existing oscillations).

In addition to its role as an internal sleep facilitator [177], melatonin acts as an antioxidant, anti-inflammatory and neuroprotective agent [89, 100, 181]. Several lines of evidence suggest that melatonin could also modulate neuronal networks in several brain areas. Besides the SCN [182], melatonin was shown to act in the hippocampus, first modulating memory consolidation by phosphorylation of CREB (CRE-binding protein) modulation through a mechanism involving MT1 receptor [182, 183]. Second, melatonin significantly inhibits synaptic transmission and long-term potentiation (LTP) in the hippocampus through a mechanism involving MT2-receptor [184]. Indeed, melatonin seems to modulate day/night variations in glutamate and GABA systems, known to be involved in ASD [185]. Altogether, several lines of evidence highlight that melatonin may act in different receptors for controlling functional responses, which opens perspectives for the use of selective melatonergic-system based drugs.

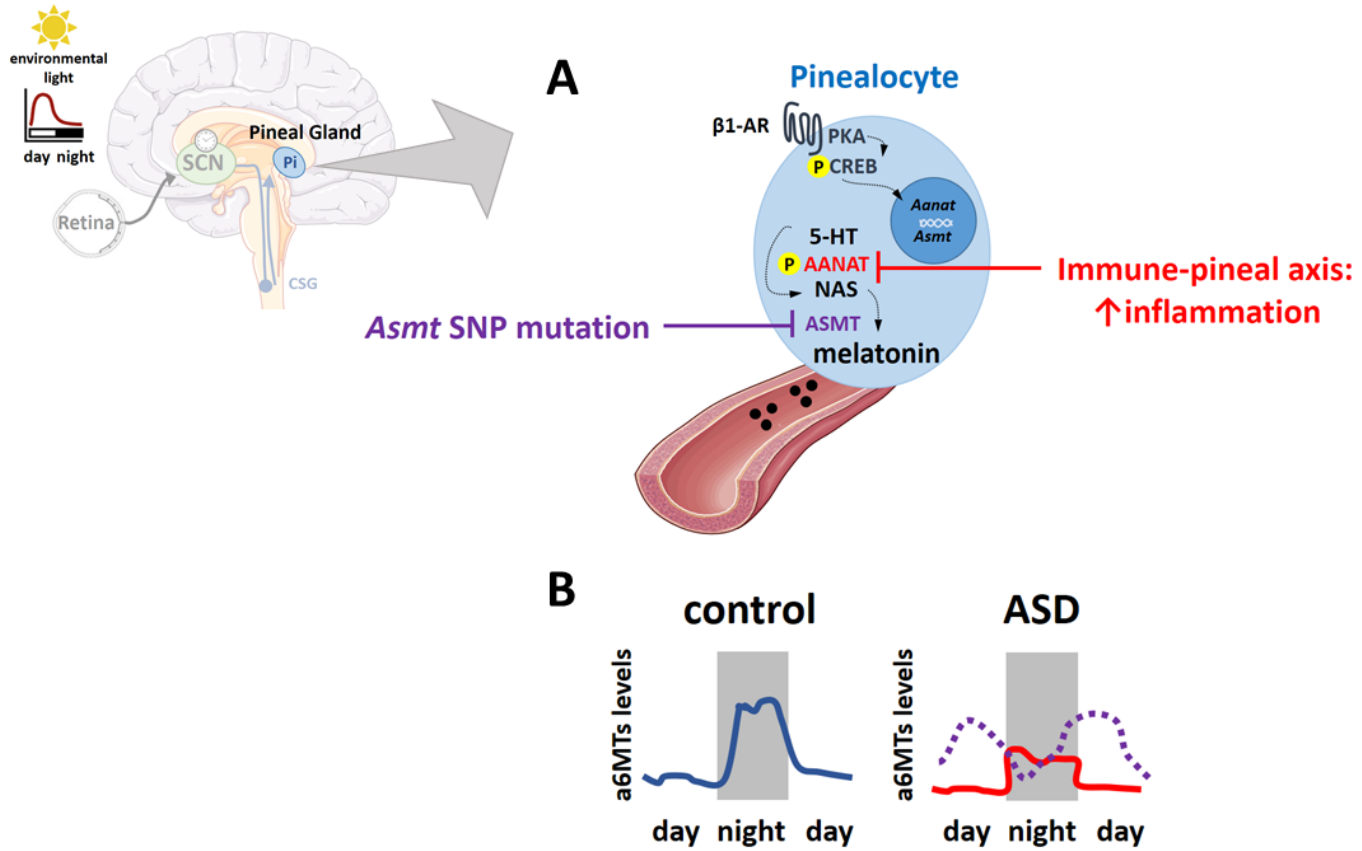

Fig. (2). Melatonin production in ASD subjects: A) The regular nocturnal synthesis of melatonin, observed in individuals with normal-development, occurs based on the nocturnal release of norepinephrine directly into the pineal gland at darkness. Activation of beta 1- adrenoceptors (β1-AR) activates the intracellular cascade of the protein kinase A (PKA), a family of enzymes whose activity is dependent on the cellular levels of cyclic AMP (cAMP), and the cAMP response element-binding protein (CREB), a nuclear transcription factor that induces the expression of the enzyme aralkylamine N-acetyltransferase (AANAT). The gene coding for acetylserotonin O-methyltransferase (ASMT) is thought to be constitutively expressed in the pinealocytes. Thus, by a two-step enzymatic action, the serotonin (5-HT) levels in the pinealocytes are readily metabolized by AANAT to produce N-acetylserotonin (NAS) which is readily methylated by ASMT to form melatonin. Because melatonin is highly amphiphilic, it flows through the pineal gland recess to reach the cerebrospinal fluid and the circulation as means of the pineal gland activity. Activation of the immune-pineal axis was shown to be a major regulator of the transcription, and protein availability, of the enzyme AANAT. ASD individuals present high levels of the cytokine tumor necrosis factor, which is correlated with the reduced production of melatonin. On the other hand, single-nucleotide polymorphisms were also described for the gene coding for ASMT in ASD subjects. B) individuals with normal-development present a high urinary excretion levels of 6-sulfatoxymelatonin (a6MTs), suggesting a high fidedignity between the nocturnal production and excretion of melatonin metabolites (blue lines). Conversely, a6MTs levels in ASD is reduced (red lines) or even a phase-shifted excretion levels, suggesting that reduction of the nocturnal melatonin is impaired. Indeed, a6MTS rhythmic alterations were correlated with the activation of the immune-pineal axis. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

It is important to consider that brain structures and brain function development usually possess a dynamic function dependent on genetic and environmental cues, which lead to the maturation of new functions, or elimination of unused ones [51]. In pre-, and early- post-natal period, a critical phase of plasticity in the cortex widely contribute for allowance of neurodevelopmental disorders. This is known when the failure in coordinate maturation of neurons, by changes in timed clock gene oscillation in the SCN [53] as well as by deficits in circulating melatonin levels [186] which reinforces the need for understanding the effects and the signals transduced by melatonin in this areas in other to prevent or surpass the intrauterine or post-natal challenges in the neurodevelopment of ASD, which may find in the analysis of TNF/melatonin correlation, a mathematical model for early assessing changes observed in late-infancy alterations observed in our population of ASD patients. Thus, by detecting changes in melatonin rhythm in the early development due to increased TNF, for example, would provide further tools for assessing the beneficial pharmacological roles of melatonin in the control and management of sleep disorders observed in ASD subjects.

Altogether, our data reinforce that melatonin disruption in ASD subjects may interfere with sleep as a result of a previous pro-inflammatory phenotype. Also, increased inflammation could be also responsible for the malfunction of the SCN-driven desynchronization, which would also affect the circulating melatonin levels. This hypothesis could be the basis for understanding why melatonin therapy was shown to improve sleep quality, as well as several other aspects of behavior in ASD [26, 155]. From the earliest studies testing the efficacy of melatonin in ASD [119, 157, 187] all sleep parameters (sleep latency, waking per night, total sleep duration) are improved after treatment with melatonin subsequently improving behavior in the children and caregivers' quality of life [20, 26, 119, 155, 188].

The current practice holds that behavioral interventions including sleep hygiene, should be the first-line approach for treating sleep problems [188]. Indeed, there is a strong consensus among researchers that exogenous melatonin is beneficial and safe for treating chronic sleep disorders in ASD children [119, 161, 188, 189]. The treatment with melatonin, behavioral interventions, and

parent education/interventions seems to be the most effective at ameliorating multiple domains of sleep problems [189].

It is relevant to highlight that in addition to the infants, whose present reduced levels of melatonin, the mothers of ASD subjects also have decreased levels of melatonin at night [160]. One could argue a relationship between maternal nursing and ASD patients; however, no study has provided clear evidence for increased susceptibility for having ASD offspring dependent on the reduced nocturnal melatonin levels. This can result in a circadian dysregulation of both mother and children since the daily variation of melatonin levels is one of the factors that sets the SCN to a 24-hour cycle and therefore is crucial for appropriate regulation of several physiological rhythms including sleep/wake cycle. Indeed, albeit glucocorticoids, melatonin is a well-known hormone to feedback to the SCN and reset the oscillation of the clock gene machinery [174, 190]. Because the increase in sleep propensity [191] and the reduction of body temperature [192] at night should occur after the nocturnal melatonin rise, lack of melatonin at night may affect the adjusting of the temporal organization at several physiological processes, such as immune responses [193], energy metabolism [194] and proper neural function [100].

Indeed, several aspects of body physiology occur under the daily synchronicity driven by melatonin. In metabolism, the decreased melatonin has consequences for energy homeostasis and the local temporal-controlling system [190]. Mice lacking both MT1 and MT2 receptors show alterations in the daily profile of clock gene expression in the pancreas and the liver [195]; Furthermore, pinealectomy impairs insulin sensitivity and gluconeogenesis [196]. Thus, impacting melatonin production also has consequences in energy homeostasis. Regarding the regulation of immune functions [96, 97] long-lasting disruptions of melatonin signal suppress clock gene oscillation in the spleen, a pattern currently observed in diabetes, and neuroinflammatory responses [197] suggesting that the fine-tuning of the rhythmic nocturnal production of melatonin is important for the maintenance of several aspects of human physiology. Melatonin also regulates the functional activity of pituitary *pars tuberalis* through MT1 receptors, which transmit signals controlling the production of thyroid hormones, as well as to prolactin secretion [198]. Lack of neuroendocrine responses of melatonin is also related to increased lipogenesis [199] and the regulation of peripheral oscillation of the clock gene expression in the adipose tissue [200].

Altogether, we have reviewed the major contributions of the circadian rhythms in the normal-developed subject and ASD individuals. We discussed that ASD individuals might have several points of impairment of brain development and maturation within the control of areas that regulate circadian rhythms. Two pivotal areas, the SCN and the pineal gland, are two target areas of the brain, interconnected, that drive several aspects of the human rhythms, which has consequences for behavioral phenotypes, including sleep regulation, memory formation, immune quiescence, and metabolic fitness.

Our current hypothesis highlights the need of the early diagnosis of simultaneous measures of melatonin and TNF, which may be achieved by non-invasive methodology, and thus, improving the data for supporting clinical pharmacological intervention based on melatonin or analogs to improve the well-known outcomes of neurological disturbances observed in ASD subjects, as sleep disturbances, deficits in cognition and behavioral issues.

CONCLUSION

Current evidence supports the existence of associations among ASD, clock gene mutations, abnormal rhythmic secretion of melatonin and glucocorticoids, sleep disorders, behavioral problems, and increased inflammation. Although the direction of causality remains elusive, much of this evidence can be correlated based on lack of nocturnal melatonin production, as exogenous melatonin improves sleep, synchronizes clock gene expression in several tissues, and regulates the immune system. Correlational evidence calls for improving the diagnosis regarding the chronobiological aspects of ASD, which includes beneficial aspects for improving the detection of behavioral problems, aspects of the daily activities and a clear track about the drugs in use along with non-obvious aspects of ASD treatment, including timely use of melatonin and analogs, which could complement the treatment of ASD.

LIST OF ABBREVIATIONS

AANAT	=	aralkylamine N-acetyltransferase
ACTH	=	adrenocorticotropic hormone
ADHD	=	attention deficit hyperactivity disorder
aMT6s	=	urinary 6-sulfatoxymelatonin
ASMT	=	acetylserotonin O-methyltransferase
cAMP	=	cyclic adenosine monophosphate
CSF	=	cerebrospinal fluid
CREB	=	cAMP response element-binding protein
FMR	=	fragile X mental retardation
LPS	=	lipopolysaccharide
LTP	=	long-term potentiation
NAS	=	N-acetylserotonin
NF-κB	=	nuclear factor kappa B
NPAS	=	neuronal PAS domain protein
NR1D1	=	nuclear receptor subfamily 1, group D, member 1
NREM	=	non-rapid eye movement
PKA	=	cAMP-dependent protein kinase
PKC	=	protein kinase C
PVN	=	paraventricular nucleus
SCG	=	superior cervical ganglion
SCN	=	suprachiasmatic nucleus
SNP	=	single nucleotide polymorphisms
SWS	=	slow-wave sleep
TNF	=	tumor necrosis factor
TPH	=	tryptophan hydroxylase

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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