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Chronobiology of Autism Spectrum Disorders (ASD)

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ABSTRACT

Autism Spectrum Disorders (ASD), is a neurological disorder that primarily affects children throughout their formative years. This complex heterogeneous disease is characterised by impairments in social interaction, incorrect communication, and behavioural difficulties, as well as significant influences on cognition, environmental, and hereditary variables associated with this recessive disorder. A review abstract of the PubMed database and used keywords were "Circadian rhythms" AND "Autism" AND "Genetic mechanism of ASD". The development of the infant/child is linked to the mother's circadian rhythmicity throughout pregnancy, according to the research evaluation. Autistic people appear to have ultradian cycles rather than circadian rhythms, which impacts melatonin regulation, possibly as a result of pineal hypo function, and thus helps to alleviate the disorder's symptoms. A relationship between synaptic genes and clock genes has also been uncovered as part of the investigation into the origins of this sickness. Autistic people often have sleep problems as a result of their frequent waking and unwillingness to sleep. ASD has been caused or worsened by mutations in clock genes such as per, clock, cry, ck1a, dbp, and Npas. Circadian abnormalities during crucial phases of brain development could be linked to early development concerns and their potential integration with ASD. ASD is thought to be caused by inflammatory, metabolic, environmental, and inherited variables, as well as characteristics associated with sleep disorders, but definite causes have yet to be identified. Sleep disturbances, circadian unrhythmicity, and melatonin synthesis, regulation, and function impairments are prevalent abnormalities noticed not only in autistic patients' development, but also in their parents' and family members' daily lives. The disease's course is influenced by circadian rhythms, the sleep-wake cycle, and related hormones, as well as hereditary and environmental variables.

Keywords: *Autism, neuropsychiatry, sleep-wake rhythms, ultradian rhythm*

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INTRODUCTION

Autism Spectrum Disorders (ASD) is a multifaceted neurodevelopmental illness characterised by symptoms such as non-interactive behaviour and a lack of awareness that worsen with age, posing a threat to a child's development and maturation [1]. It's a brain-development disorder that affects how a person perceives and interacts with others; resulting in social and communication problems [2] Features of the syndrome include limited and repetitive patterns of behaviour [1-4]. Autistic Disorder, Asperger's Disorder, Rett's Disorder, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder-Not Otherwise Specified are the five types of autism spectrum disorders (PDD-NOS) [4]. ASD is known to run in families, but the inheritance pattern is indeed unknown [5]. Some of the factors that contribute to the onset or intensification of ASD symptoms entail nutritional deficiencies or overloads, complex genetic interactions, the mother's health, the mother's age, exposure to chemicals, viruses, heavy metal toxicity, immunological overload due to vaccinations, food additives, and dysfunctional immune systems or allergies [6-7]. Atypical speech patterns and tone of voice, late development of speech skills, difficulty maintaining or responding to conversation, limited eye contact, limited response to social interaction, repetitive speech and behaviour patterns, and difficulty understanding other people's feelings and intentions are among some of the characteristics observed in autistic diagnosed individuals [8]. Autism is typically diagnosed in childhood or within the first three years of life [9]. It's a disorder in which kids

can't read other people's emotions and can't tell the difference between aggression, grief, and manipulative intent. Their inability to start or maintain conversations, their poor language skills, and their excessive obsession with a particular subject, activity, or gesture characterize such youngsters [1-4, 8,10-11].

Autism was once understood to be a complex psychiatric or developmental disorder with the most clinically supported diagnostic criteria across countries. Autism is becoming more widely recognized as a phenomenon [12]. Autism can be diagnosed based on theoretical reasons and some known comorbidities, such as epilepsy or mental retardation [11-12]. Autism was originally classified as a Pervasive Developmental Disorder (PDD) with problems in verbal and nonverbal communication, as well as social connections, and is characterised by repetitive and compulsive behaviour, speech repeats (Echolalla), and a focus on similarity [1-8]. Autism's biological reasons were initially focused on four key areas: neurology, biochemistry, genetic abnormalities, and pregnancy issues [6]; as a result, it is regarded as a complex and difficult condition [1-13].

The functionality of the body affects several biological cycles [14]. This physiological rhythm is further characterised as ultradian, tidal, circadian, lunar, and seasonal rhythms based on the temporal scales or distinct time scales [14-16]. The circadian rhythm is the best researched of all the major rhythms. Circadian means around a day and it is a cycle of a 24 hour, that is, a day and corresponding to a 24 hour light dark cycle of the earth's rotation [17-18]. It is only the circadian rhythm that helps govern the majority of biological and behavioural functions [1], and disruptions in this rhythm result in sleep disorders [19] and changes in physiological activity [20]. This circadian rhythm is formed in mammals by a master central clock, which is mostly reset by ambient light and is located in the hypothalamic suprachiasmatic nuclei (SCN) [21]. Direct or indirect signals (cycle hormone production) exchanged between suprachiasmatic nuclei and other physiological components regulate all biological activity 24 hours a day, seven days a week (brain regions, organs) [21,22]. Each organ in the body (heart, lung, liver, muscles, kidneys, retina, and so on) contains peripheral clocks that optimize each organ's performance in reaction to the external context, allowing the organism to adapt to environmental changes [1, 23]. As a result, the circadian clock network serves as an adaptive mechanism [21-23].

Autism is frequently observed in conjunction with other disorders or symptoms affecting the central nervous system (CNS) [2]. Previously troublesome areas in the brain include the cerebellum, limbic system, cortex, and a lack of brain lateralization [3-5]. According to a case study, sleep difficulties, in addition to the most common co-occurring illnesses in ASD, are a likely reason that exacerbate associated behavioural disorders and contribute to the aggravation of existing autistic symptoms [24]. ASD is a neurodevelopmental disease characterised by a loss in social interaction and communication, as well as the appearance of repetitive behaviours and restricted interests in early childhood [7,8]. Prevalence of sleep disorders, decreased melatonin secretion- lower nocturnal and diurnal levels of melatonin, melatonin changes, and disrupted sleep wake pattern suggest that diagnosed patients have or follow alternate circadian rhythms [24]. This pattern indicates that they may adhere to either ultradian or infradian cycles [1].

Melatonin secretion has a circadian rhythm and is regulated by the light/dark cycle; light suppresses melatonin production, and with the arrival of darkness, melatonin is generated and secreted from pinealocytes [15,25]. The retinohypothalamic tract transmits light input from the retina's photic receptors to the suprachiasmatic nucleus (SCN), which is located in the anterior hypothalamus and serves as the body's major circadian pacemaker [17]. During the night, the SCN induces the release of norepinephrine from the superior cervical ganglion; norepinephrine stimulation of pinealocytes results in the generation and release of melatonin [17-19,26].

Melatonin is not retained in the pineal gland, but is discharged as soon as it is produced [26,27]. The hormone is most likely secreted into the bloodstream before entering the third ventricle's cerebrospinal fluid (CSF), although it could possibly be secreted directly into the CSF [28]. Melatonin levels in CSF are significantly greater than in plasma, providing evidence for direct secretion of melatonin into CSF [29]. Melatonin can also be detected in saliva, where levels are around 70% of those seen in plasma [29]. Melatonin release begins at 2200–2300 hours and peaks in plasma concentrations around 0300–0400 hours during a normal sleep cycle [30-32]. Melatonin secretion is offset at roughly 0700–0900 hours[33].

Many researches have shown that the prevalence of sleep disorders in ASD is 50-80 percent when compared to the normal/control group of individuals in their various methodological studies [34, 37]. Sleep issues and a dysregulated sleep-wake pattern are not confined to ASD patients; the disturbed sleep-wake cycle is also reported in ASD children's parents [38, 39]. Melatonin is a crucial hormone in the sleep-wake cycle and circadian rhythmicity, and it plays an important role in maintaining the body's circadian rhythms synchronized with the environment with the help of zeitgebers [27]. Sleep is a common physiological event that affects our basic physiological functions (e.g., metabolism, immune system),

behaviour, cognition, and emotion in a vast, pervasive, and cyclical way [40]. Neurotransmitters, immunologically active peptides, and hormones all have a role in sleep, which is mediated by complex interconnections [41]. The immune system and sleep are related in both directions [40]. Low levels of melatonin secretion have been discovered to be a common feature in ASD patients, including nocturnal and diurnal cases [42-45]. There are subjective studies that show that using melatonin as a therapeutic drug can help affected children/adults, but the cause of the consequence between melatonin and ASD is still unknown, so it all proves that clock and circadian regulations play a role in ASD, though the mechanism is still unknown [39, 42,46-47].

THE CIRCADIAN CLOCK

Humans have homologues of the clock, Bmal1, Per, and Cry genes [48]. Clock, the only cloned circadian rhythm gene, is located on chromosome 4 [49]. Retinoic acid receptor-related orphan receptor (ROR)-A and ROR-B, REV-ERB, and casein kinase-1 (Ck1) and Ck1, which impact Bmal1 transcription, are all clock genes implicated in circadian control [17,18]. In addition, the albumin-D-site-binding protein (Dbp) is a circadian clock-controlled gene that regulates the transcription of a variety of metabolic enzymes and transcription factors [50,51]. Mutations in certain clock genes, such as per, clock, cry, ck1a, dbp, and Npas, modify sleep homeostasis markers, whereas an increase in homeostatic sleep drive changes clock gene expression in the forebrain [35,36, 52].

Chemical processes that generate circadian rhythms are very similar across species [53]. Among these are promoters, repressors, and regulatory loops involving phosphorylation-dephosphorylation, methylation, acetylation, and specific protein dimerization. The hypothalamic central clock, suprachiasmatic nuclei, and secondary clocks in the brain and peripheral organs together comprise this molecular circadian system in mammals[14,54]. The master clock's transcription of certain genes of the circadian rhythm changes in response to light received by the retina, exhibiting the body's ability to adapt to a change in the photoperiodic environment's cycle [55]. Many peripheral circadian oscillators are synchronised by this master clock using techniques that are unknown at this time [53-55].

In general, the circadian clock molecular loop appears to indicate two types of mechanisms: transcriptional (gene transcriptional regulation at the DNA level, i.e., their copy in the form of RNA messenger) and post-transcriptional (gene transcriptional regulation at the RNA level, i.e., their copy in the form of RNA messenger) mechanisms (regulating steps downstream of the transcription) [56,57]. These systems can be summarized using autoregulatory feedback loops [58] . The first autoregulatory feedback loop is a large negative feedback loop that is dependent on two positive elements (the heterodimerizing transcription factors CLOCK and BMAL1) and two negative elements (two proteins, PERIOD (PER) and CRYPTOCHROME) (CRY) [59].

In a suprachiasmatic nucleus neuron, the CLOCK–BMAL1 complex stimulates the transcription of Per and Cry genes to the maximum degree possible [54, 58]. The PER and CRY proteins, however, do not accumulate certainly due to their instability; instead, they gradually stabilise during the day, then heterodimerize and migrate into the nucleus, where they inhibit the transcriptional activity of the CLOCK–BMAL1 heterodimer and thus their own transcription [56, 57, 59] refer to figure1 here. The PER and CRY proteins become less abundant as the Per and Cry genes become less active. Their quantity peaks early in the evening and then gradually decreases. The CLOCK–BMAL1 heterodimer, on the other side, gradually reactivates during the night [59].

In many peripheral tissues, CLOCK and BMAL1 heterodimers are also involved in the daily transcription of several clock-controlled genes (CCGs), and the orphan nuclear receptors REV-ERB and ROR form another regulatory feedback loop [20, 60]. In the nucleus, REV-ERB competes with ROR for binding to the Bmal1 promoter's ROR-responsive element (RORE). REV-ERB reduces Bmal1 transcription, whereas ROR stimulates it [50, 56]. As a result, both positive and negative regulation of RORs and REV-ERBs is required for cyclic expression of Bmal1 [59- 61]. This supplementary feedback loop is known as the "stabilising loop [1].

Several post-transcriptional processes alter PER and CRY's ability to function on CLOCK and BMAL1 [14]. The most researched characteristics of these proteins are the phosphorylation and dephosphorylation. Several kinase proteins target PER and/or CRY, and each of the two proteins can be phosphorylated multiple times [54, 60, 62]. They either speed up or slow down the transport to the proteasome. Ubiquitin "tags" proteins that need to be destroyed. The clock proteins in the main molecular loop are controlled post-transcriptionally, ensuring intracellular traffic, function, and degradation, which are all essential for the molecular loop to function for 24 hours[1].

Core body temperature, neuroendocrine activity [63], cardiovascular function [64], and sleep-wake cycle time [35] are all regulated by the circadian timing system. Endogenous melatonin, which is generated by the pineal gland at night and functions as a time signal to stabilise and synchronise the levels of

expression circadian rhythms, regulates the sleep-wake cycle [65]. Two significant circadian anomalies have been found in children with ASD: phase delay of sleep periods and an irregular sleep-wake cycle [37, 66-69]. This possible anomaly has been linked to alterations in the expression of the clock genes of the circadian clock.

Melatonin and its regulation in ASD fetus and neonates

Melatonin is a model for medications that alter the circadian apparatus (Chronobiotics) and plays an important role in the coordination of circadian rhythmicity [70]. It is a powerful cryoprotective agent with high antibacterial properties [26]. It also has anti-oxidant [71,72], anti-inflammatory, antiviral, immunostimulatory, and immunoregulatory properties [73]. Even with high melatonin doses and the use of a fast release preparation administered at a single point in the day (bedtime), the chronobiotic effects are retained [70]. Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone produced mostly by the pineal gland, which is located behind the third ventricle in the brain [74]. During the formation of melatonin, tryptophan is hydroxylated to 5-hydroxytryptophan, which is then decarboxylated to 5-hydroxytryptamine (serotonin). Serotonin is converted to the melatonin precursor and metabolite N-acetylserotonin by the enzyme N-acetyl transferase. Melatonin is made by the enzyme hydroxyindole-o-methyltransferase methylating N-acetylserotonin, refer to figure 1. Hepatic microsomal enzymes convert melatonin to 6-hydroxymelatonin. The majority of the latter product is conjugated with sulphate to produce 6-sulfoxymelatonin before excretion in the urine, while a little quantity is conjugated with glucuronide [37, 75] .

Serotonin, a precursor to the circadian neurohormone melatonin, has been implicated in a variety of functions including sleep, circadian rhythms, affective modulation, and stereotypic behaviour [46, 76]. Patients with ASD have previously been found to have higher whole blood serotonin levels and lower plasma melatonin levels [77]. The efficacy of drugs that limit serotonin transport, as well as an aggravation of these behaviours after pharmacological depletion of tryptophan, which leads to lower serotonin synthesis, support the relationship between serotonin levels and behaviour [78,79].

Circadian rhythms influence the synthesis and production of melatonin, a hormone [44]. Melatonin is a hormone that peaks in the middle of the night, about 2 to 3 a.m., and then drops during the day [75, 80]. Melatonin is predominantly generated by the pineal gland; however there are several additional hormones that are known to participate in the synthesis of melatonin, including the retina, Harderian gland, gut, bone marrow, platelets, glial cells, lymphocytes, pancreas, kidneys, and skin [81]. It is involved in a variety of biological processes, including the control of circadian rhythms [44] and sleep [82], anticancer [83], metabolic effects [82], anti-inflammatory functions [73], and antioxidant effects [71,72], as well as a critical part in embryonic development [6, 84-86].

ASD is a neurodevelopmental disorder, which means that the disorder's generation/introduction begins during the developing phases, and so a link between the mother and fetus can be established [47]. Melatonin also plays a role in fetal development, but the main source of melatonin production, the pineal gland, matures only after birth, so during the fetal stage, the fetus uses maternal melatonin, which retains the property and capability of crossing physiological barriers, including the blood placental barrier, without denaturation and thus influences placental function [84]. As a result, during pregnancy, melatonin crosses the placenta and enters fetal circulation, where it continues to send photoperiodic information to the fetus, and now the mother's melatonin regulates the circadian rhythms of her children [84, 87].

Certain circumstances, such as jet lag, shift work [88], and melatonin levels [89], can disrupt circadian rhythms. Circadian disruptions and neurodevelopmental problems are both linked to aberrant melatonin output [90]. Melatonin's antioxidant and direct free radical scavenging properties are widely recognized, as evidenced by a human investigation that indicated that increased nighttime serum melatonin was associated with antioxidative activity [71-72]. Melatonin may play a role in the development of the nervous system [6]. A proper sleep pattern is critical for optimal neurodevelopment, and disrupted circadian rhythms, which could be caused by aberrant melatonin levels, can stunt brain growth and raise the risk of ASD [89]. As a result, ASD is linked to low melatonin levels and sleep difficulties. ASD sufferers rely on sleep issues such as difficulty getting to sleep, falling asleep, and even increased sleep latency [91]. Melatonin injection before to sleep enhances sleep efficiency in ASD patients, making it the most effective treatment for ASD among numerous alternative causes [92]. The NAS and N-acetylserotonin methyltransferase genes are highly heritable, and the findings suggest that melatonin synthesis anomalies in patients with ASD are inherited [6, 47, 30]. Low paternal melatonin levels have been linked to an increased risk of ASD in offspring, emphasizing the importance of melatonin during fetal neurodevelopment [89]. Parents of children with ASD typically report that parenting children in the neonatal age is more difficult since these children have sleep challenges, according to common clinical practices associated to developmental disorders [47]. Based on ASD symptoms, neonatal are classified

into two types: irritable or overactive, where the conditions observed are frequent waking, difficulty falling asleep, short sleep amounts, and continuous crying and grumpiness, and apathetic or under reactive, where the conditions observed are those who sleep continuously when they go to sleep and no frequent waiting is observed in under reactive neonatal [47]. Sleep-wake rhythm abnormalities in neonates may be significant predictors of future ASD development. ASD is most likely caused by genetic and environmental factors. The bond between the mother and the fetus throughout pregnancy is crucial to chronobiology [87]. The fetal period is when the circadian cycle begins to build, and there is no relationship between the ultradian period and the time of day, according to chronobiology. The ultradian cycle, which has 3 to 4 hour sleep wave patterns, governs a neonate's daily life [93]. The ultradian rhythm regulation centre is located in the pons and medulla oblongata areas of the brain [87].

Problems in Toddlers/Children of Autistic traits

Sleep difficulties are one of the most common comorbid disorders associated with ASD [94]. Sleep issues may precede and exacerbate the behavioural manifestations of ASD [94]. When compared to toddlers without autistic features, autistic toddlers are more likely to demonstrate (1) bedtime resistance, (2) abnormal circadian rhythms, and (3) sleepiness outside of napping time. Anxiety, poor sleep hygiene, sensory hyper-sensitivities, anomalies within the melatonin system (i.e., circadian rhythm), and obstructive sleep apnea have all been linked to sleep disturbances in children with ASD according to previous studies [94-95]. Sleep difficulties in people with ASD are linked to biological causes, according to other investigators [6]. Children with ASD may have a disturbance of sleep homeostasis, which manifests as a drop in sleep pressure [96]. Genes may be involved in synaptic homeostasis, including synaptic growth and pruning, which could be a factor in both ASD and sleep-wake control [96]. Sleep disorders may co-occur with autistic features in early childhood, according to findings involving behavioural, physiological, and biochemical aspects. The findings of one study support that sleep issues may be a probable pre-comorbidity in ASD [94]. There seems to be evidence that people with ASD have greater incidence of sleep issues, seizures, sensory impairments, atopy, autoimmune illnesses, and obesity when compared to the general population [97]. In children with intellectual impairments and ASD, having more sleep issues is linked to having more anxiety [95]. Sleep issues can also be indicated by avoidant behaviour and under-eating [98]. The discovery of a relationship between comorbid psychopathology and sleep disorders will have ramifications for treatment outcomes, and comorbid psychopathology treatment may affect sleep problems. Treatment of sleep disorders, on the other hand, may result in a reduction in concomitant psychopathology symptoms [98].

Sleep disorders in children with ASD are linked to a slew of emotional and behavioural issues, but the mechanisms underlying how sleep influences daytime behaviour are unknown. Autonomic dysfunction (i.e., increased sympatho-thetic drive and physiological arousal as indexed by heart rate, cortisol, or skin conductance) is a potential mechanism of influence, according to behavioural theories, sleep theories, and previous investigations [99]. The potential linkages between sleep and daily autonomic function have been highlighted in research on sleep and EDA in normally developing humans and people with disturbed sleep or ASD [94-96,98]. Understanding these extended patterns of EDA and sleep for children could be particularly informative in the context of sleep, given that sleep is a malleable biosocial process and could be a therapy target to improve daytime arousal profiles, according to one study, which aims to move the field forward by providing the first 'in the wild' extended recordings of EDA and sleep for children with ASD [99], in this study children in the Dysregulated Sleep (DysS) group showed a trend of lower physiological arousal, which was particularly noticeable in the afternoon, whilst children in the Regulated Sleep (RegS) group exhibited higher EDA indices. According to the findings, physiological arousal levels in children with ASD may follow a circadian pattern and may be influenced by sleep dysregulation or a dysregulation profile [96,99]. Sleep deprivation can make it difficult to fully recover during the night, and it can also lead to changes in physiology following morning.

ASD is a genetically and phenotypically heterogeneous condition that frequently co-occurs with other medical and behavioural issues [13]. Autistic children and adolescents experience chronic sleep problems at a higher rate and severity than ordinarily developing children and those with other developmental disorders [94-97,99f]. Sleep disturbances are reported by the majority of parents of autistic children, including 53% of parents of early autistic children aged 2–5 years and 66.1 percent of parents of autistic children aged 4–10 years [98]. de novo likely gene-disrupting mutations (dnLGD) CHD8, ADNP, and DYRK1A have been discovered as potential genes for ASD, and their phenotypic profiles appear to be distinct [96]. The gene Chromodomain helicase binding protein (CHD8) is involved in chromatin remodelling and is thought to be vital for neuronal cell proliferation and control. Individuals with ASD and CHD8 mutations have also been observed to have severe trouble falling asleep and/or staying awake for days at a time [100]. DYRK1A (Dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase 1 A)

has been connected to cellular signalling and brain development, and persons with DYRK1A mutations have been observed to suffer frequent overnight awakenings [100-102]. Cellular differentiation and maturation are aided by the activity-dependent neuroprotective protein (ADNP) gene [103]. Although particular sorts of sleep problems have yet to be reported, general sleep issues have been frequently recommended for children with ADNP mutations [104]. Autistic people spend less time in rapid eye movement sleep than non-autistic people, according to studies [105], but the results were inconclusive [106]. Fundamental neurotransmitters such as dopamine, serotonin, and GABA, which have been proven to be critical in sleep regulation, are altered in ASD on a molecular level [107]. The magnitude to which these brain pathways are compromised and sleep is disrupted varies greatly among autistic people. This study mentioned that in comparison to the other interest and control groups, the ADNP profiles showed much more sleep disorders, including breathing problems and more daytime naps, for ADNP and CHD8, frequent overnight awakenings were more supported compared to the control group and compared to the control group, the CHD8 had greater difficulty falling asleep and required the parent to lie down with the child. With the exception of increased difficulty breathing at night, higher daytime naps, and no issues with sleepwalking, the DYRK1A group did not differ significantly from the control group [96]. We came across a study when doing research for this review that looked at the effects of an exogenous dose of melatonin on ASD patients, particularly young children, and their responses to it. The behavioural therapy package was very effective in minimising sleep latency and night voids in young children with ASD, according to the findings of this study [98]. While not all of the children's sleep difficulties were entirely resolved, the benefits were significant, particularly for the parents of the patients. Because this study used actigraphy, which tracks light and motor activity to assess sleep wake patterns and typically transcripts more night awakening, which parents also reported in the form of sleep diaries, the objective data was helpful in providing robust data for comparison with the sleep diary data [98].

In children, a 60-75 minute interval is equivalent to at least one complete sleep cycle, which includes both REM and non-REM sleep (around 50 to 80 minutes, depending upon the age). Both REM and non-REM sleep are linked to childhood development and memory consolidation [108-109]. It's also well established that consolidated sleep over the course of the night is best for the plasticity changes required for learning and memory consolidation in children with ASD [110]. In a few studies, it was discovered that a long duration of sleep episodes following a few months of melatonin administration resulted in a considerable shift and improvement in the daytime behavioural difficulties of ASD diagnosed children [98, 111]. Furthermore, this longest leap phase improves the quality of life of the parents of the ASD identified children [35].

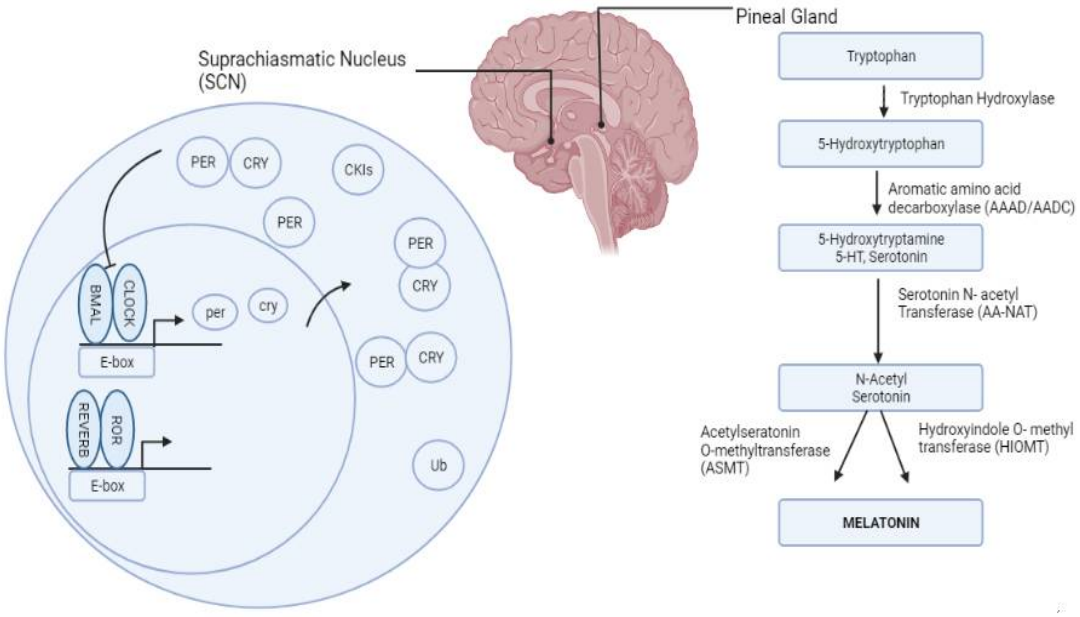

Figure1: This figure is representing the molecular mechanism of circadian clock of a human as well as the pathway of the synthesis of the melatonin.

CONCLUSION

Most species on this planet are vulnerable to predictable changes in light and temperature as a result of the Earth's rotation around its axis every 24 hours. Endogenous biological clocks have developed in a

wide range of animals, from cyanobacteria to humans, to allow for the anticipation of these daily fluctuations. As a result, our interior physiology and function are intrinsically linked to the geophysical cycle. The study of biological processes in relation to time, with a focus on the four environmental rhythms of tide, day, moon, and season, is known as chronobiology. This geophysical cycle is deeply interwoven with our own physiology and function. Franz Halberg in 1959 coined the term "circadian" (Latin: circa = about; dies = day) to refer to daily rhythms that are actually endogenously generated, that is, rhythms with a period of roughly 24 h that continue to fluctuate in the absence of any environmental input, to underline the endogenous or self-sustained nature of biological clocks. Single cells generate rhythms as a result of an intracellular molecular oscillator based on transcriptional/posttranslational negative feedback loops. These endogenous oscillations are normally synchronised with the environment, and biological clocks are assumed to give an adaptive benefit by ensuring that an organism's internal biochemical and physiological processes, as well as behaviour, are appropriately matched to the local environment. Circadian rhythm research has revealed how biological processes combine to generate daily rhythms in physiology and behaviour in a wide range of organisms and species, with the potential to improve fitness and human health. Disruption in daily or circadian cycles may increase the risk of noncommunicable diseases, but if the desynchronized rhythms persist for an extended period of time, it may also result in neurological and neurodevelopmental issues. ASD is also thought to be a rhythmicity condition, referring to problems with rhythm synchrony. Asynchrony may be crucial in the pathogenesis of ASD. Sleep is frequently affected in people with ASD. In this day and age, when the prevalence of ASD problems is quickly increasing, there is an urgent need to understand the mechanisms involved in the pathogenesis and development of ASD. Circadian biomarkers, sleep-wake rhythms, neurotransmitters, language, communication, information processing, and daily rhythms are all connected with circadian clock function and are compromised in individuals with ASD. There are links between clock gene polymorphism, seasonal differences, and ASD. A similar correlation exists between sleep and ASD, and previous research has found that the associations between circadian dysfunction and ASD can be bidirectional as well, suggesting that circadian clock malfunctions may be one of the physiological aspects that underpin the pathogenesis of ASD, though experimental evidence for this disruption that can lead to neurodevelopmental disorders is still being researched.

The results illustrate some converging effects of circadian biomarkers, that is, melatonin, serotonin and dopamine along with the signal transduction pathways that are involved in mood, behaviour, cognition, and impaired social functions, learning and memory are affected by these neuropsychiatric disorders which can also guide brain development and sleep by turning on disturbance.

Conflict of Interest

The authors declare no conflict of interest.

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