# The Role of Circadian Rhythm in Autism Spectrum Disorder

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**Abstract.** With the development of technology and gradual enrichment in life, there is a significant increase in attention towards neurodevelopment and child health. Autism Spectrum Disorder (ASD) is defined as a neurological and developmental disorder that affects how people speak, behave, and interact with others. Communication and social interaction issues, sensory abnormalities, repetitive habits, and varying degrees of intellectual disability are some of the symptoms of autism. ASDs influences about 1 in 44 children in the USA, with the number of incidents sharply increasing over the years. Epigenetic neurobiology factors and environment related factors should both be considered when interpreting the pathophysiology that lies behind ASD. The 24-hour physiological cycle that displays an endogenous and entrainable oscillation is known as the circadian rhythm, which is generated by a molecular clock system. Mounting evidence are linking circadian rhythm disorder and autism. This includes sleep chaos as a common epiphenomenon of ASD, melatonin level disorder in ASD and circadian gene dysfunction in ASD. This article revolves around three perspectives: 1) Sleep Disorder in ASD 2) Role of Circadian Biomarkers in ASD 3) Variants and deficiency of circadian genes in ASD. In conclusion, the article reveals the important role circadian rhythm plays in neurodevelopmental processes. Through examining the circadian rhythm not only as an epiphenomenon but also as a possible indicator for ASD, the article anticipates the implication of circadian rhythm in novel treatments of ASD as a conclusion.

**Keywords:** Circadian rhythm, autism spectrum disorder, circadian rhythm disorder, treatment.

## 1. Introduction

The 24-hour solar day is how life on this planet has evolved. Circadian rhythms are the internalization of the dependable daily cycles of light and dark over the course of evolution. It serves the function of anticipating changes in the environment and prepares organisms to respond properly. The circadian rhythm is affected by environmental factor, for example, light. It remains a roughly 24 hours oscillation in virtually all physiological functions of the human body and brain. When circadian systems are thrown off by several environmental factors or genetic flaws, various physiological functions might become dysfunctional. A number of mental diseases, such as major bipolar disorder, depression and anxiety are associated with altered circadian rhythms. The molecular clock of circadian rhythm includes several Drosophila core clock protein homologues, such as CLK and PER. Increasing amounts of research has indicated a significant role for circadian regulation in gene expression (Figure 1). The majority of genes expressed in the human body, approximately 10%, are found to exhibit circadian rhythms [1]. The clock is self-autonomous in the absence of any perturbation.

The autism spectrum disorder (ASD), which include autistic disorder and its related illnesses, is characterized by varied degrees of abnormalities in social behavior, communication, rituals, as well as stereotypies. This set of illnesses, which were once thought to be caused by the environment, are now recognized to have a significant neurodevelopmental component. These illnesses are thought to exist from birth and can be identified by the age of 18 months. Studies revealing anomalies in both prenatal and postnatal brain development have proven developmental deficiencies in ASDs. The cause of ASD cannot be expounded as one factor. When evaluating the pathophysiology underlying ASD, epigenetic, environmental, and neurobiological factors should all be taken into account. The incident of ASD increases sharply over the years, with current prevalence surveys showing that 6 out of every 1000 kids are influenced by ASD [2]. ASD cannot be improved significantly overtime as shown by current studies. According to Centre of Disease 5,437,988 adults have ASD in the United

States. Notably, increase in autism severity overtime had been identified in studies. For example, it has been implied in studies that 27–29% of their subjects have a downward tendency [3]. Immense social and economic hardships will be brought affected families and society by the high frequency of ASDs. Once activated, the concentration of PER and CRY increases overtime, and eventually dimerize. In turn, they return to the nucleus and inhibit CLOCK/BMAL1 through binding to E-box, reducing downstream genes' transcriptional activity. The circles represents involved proteins, the rectangles represent genes, the black arrows represent transcriptional activation, and the black contour represents the cell and nucleus [4].

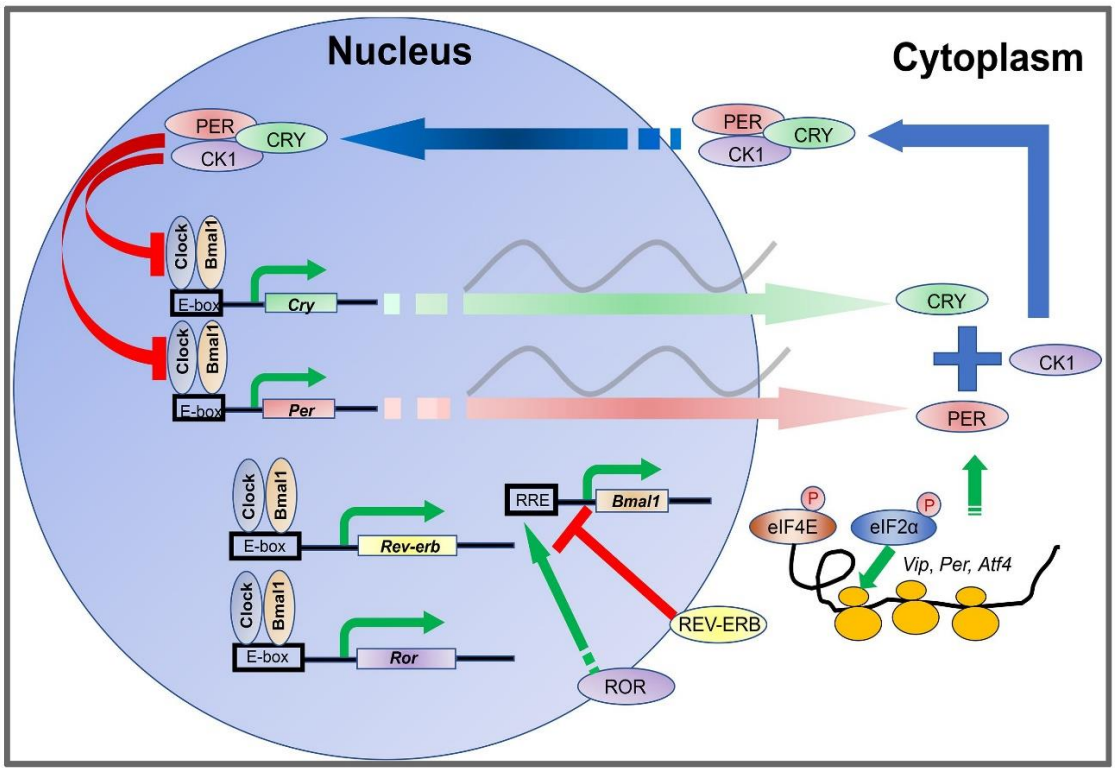



**Figure 1.** The circadian molecular clock. CLOCK and BMAL1 activate bind to E-box to start the transcription of genes Pers and Crys.

Mounting evidence perceives link between dysfunction of circadian rhythm and autism. This article examines the results from experimental and clinical research to appraise circadian dysfunction not only as an epiphenomenon of ASD, but also a possible indicator of ASD. This article first introduces circadian disruption in ASD, including sleep disorder, biomarkers disruption and variants in circadian genes. The article than identifies the adaption of circadian rhythm in novel treatments of ASD.

## 2. Sleep Disorder in ASD

Most living things seem to require sleep for life, especially for normal synaptic growth and plasticity of the brain. There is a large body of research and experiments indicating trouble in sleeping is often demonstrated in people with autism. For example, according to two research comparing the sleep habits of ASD and normally developing (TD) kids, 66% of ASD kids had moderate sleep disturbances [4]. Another research suggests that around 40–80% of people with ASD have sleep issues [4]. Additionally, sleep order in ASD is more frequent than typical groups in the majority of cases. Bedtime resistance, sleep anxiety, sleep start delay, daytime drowsiness, reduced total sleep had the highest prevalence of sleep issues among children who have autism.

The etiology of sleep disruption in ASD remains unknown. There are a number of studies that contend sleep disruption to be a result of the following: i) Dysfunction in synapse specification proteins. Synaptic cell-adhesion molecules known as neuroligins connect presynaptic and

postsynaptic neurons at synapses, regulate signaling across synapses, and specify synaptic activities to characterize brain networks. [5]. Prolonged wakefulness is related to reduction in the activity of neuroligins. NLG-1 knockout mice had a hard time maintaining alertness and spend more time in NREM sleep. Mice deficient in Neuroligin-2 sleep less overall, experience behavioral arrests that are indicative of absence seizures [6]. SHANK 3 is a gene that tethers Neuroligins and is able to enhance the dendritic spine induction and maturation. Mutation in SHANK 3 is also associated with sleep disorder. Mice who were missing both copies of SHANK has been found to sleep less generally, rarely taking naps at night and demonstrates a delayed onset of sleep [10]. Interestingly, deficiency in SHANK 3, neuroligins and neurorexins were all verified in ASD. Several studies have implicated neuroligins in ASD. The finding can be traced back to 2003, when Jamain et al detected NLGN3 missense mutations present in a case study of ASD patients [7]. Recent study found more than 30 mutations in the neuroligin genes in ASD through animal models [8]. People with ASD are also more likely to have SHANK3 mutations, as features of ASD is observed in Shank3 mutant mice. It is indicated by various studies that mutations in the neuroligin genes are relevant to the neurodevelopmental abnormalities and mental retardation in autism-spectrum disorders [9]. ii) Physiological stimulation and cognitive stimulation. Cognitive arousal in ASD is usually brought on by an increase in anxiety and can lengthen sleep latency. Physiological arousal is a result of over response to stimuli. In response to social play, children with ASD as a whole displayed relatively higher cortisol levels [10]. Both arousals can increase sleep latency and fragmented sleep in children with ASD. iii) Abnormality in hormones. Roles of biomarkers and hormones in autism will be elaborated later in the section “role of circadian biomarkers in ASD”. iv) Mutation in circadian genes. Variants in certain circadian genes such as Bmal will be discussed later in the section “deficiency and variants of circadian genes”.

It is possible that sleep disorder is not only a prominent symptom of autism, but also plays a causative role. Sleep deprivation and a delayed sleep onset are related to the intensity and breadth of autism symptoms. It can be concluded that sleep onset delay, sleep anxiety, and autism severity can all be used to predict communication symptoms, stereotyped behaviors, and social interaction deficiencies [10]. Particular focus should be placed on the sleep issues brought on by linguistic impairment additionally, since inability to express is among the most common symptoms of children with ASD [10]. Regardless, it is anticipated that novel treatments for ASD prioritize sleep disorder in the future.

## 3. Deficiency and Variants of Circadian Genes

The genetic basis of circadian rhythm was first introduced in Konopka’s study (1971), indicating Per mutations would disrupt the circadian rhythm in flies [11]. As indicated, a dozen clock genes make up and control the molecular circadian clock. As perceived by accumulated researches are suggesting that the variants of clock genes which have lost their function plays an important role in the circadian disorder of individuals with autism. The section exclusively reviews two of the prominent variations in the circadian genes related to autism.

### 3.1. Bmal 1

Haploinsufficiency in the crucial clock gene Bmal1 has been linked to ASD. Bmal1 is a protein coding gene. Complete loss of all rhythmic activities happens as a result of complete deletion Bmal1, as perceived in mice. Human sociability is linked to BMAL1 in the general population [12]. Autistic behaviors including deficits in motor learning and coordination, as well as lack of social ability are observed in mice with Bmal haploinsufficiency or complete BMAL knockout (KO) [12]. Additionally, increase in inhibitory and excitatory synaptic transmission and decreased firing rates are found in the cerebellar Purkinje cells (PC) of BMAL knockout mice [13]. Observation of mice with substitution in neuroligin-3 indicated that increased inhibitory synaptic transmission may contribute to human ASDs [14].

It's interesting to note that in Bmal1 KO mice, mTORC1 hyperactivation was reversed by the the anti-diabetic medication metformin and significantly improved behavioral and Purkinje cells impairments [15]. Due to its ability to regulating plasticity and transmission of synapse in pathological situations, anti-diabetic medication has been reported to have beneficial effects on many neurological disorders, ranging from Alzheimer's Disease to depression [15].

### 3.2. Scn2a

SCN2A has recently emerged as a prominent gene associated with sleep disorder in ASD. There are three primary sodium channels expressed in the adult CNS that regulate action potential firing, encoded by Scn2a. It should come as no surprise that these channels have crucial functions in neurons and that their mutations contribute to a variety of neurodevelopmental diseases. Analysis of deficiency of Scn2a in mice reveals that spike interval regularity was changed in Scn2a-deficient SCN neurons. This is intriguing since it has been hypothesized that synaptic plasticity, which regulates sleep, can be influenced by temporal coding [16]. Mice with a deficit in Scn2a have molecular, cellular, and behavioral changes that affect their circadian rhythm and sleep architecture [16].

However, current data is still not enough to ascertain how polymorphism in clock genes can explain the sleep abnormities associated with autism. This review calls for future research to manifest the effectiveness of this hypothesis in various neurological illnesses and diverse disease models.

## 4. Role of Circadian Related Biomarkers in ASD

During studies, levels of circadian biomarkers were measured in patients with ASD to ascertain the body clock. In this part, the changes of melatonin and cortisol, and how these changes are prominent to the symptoms of ASD are discussed.

### 4.1. Melatonin

Melatonin synchronizes both central and peripheral oscillators, allowing biological functions to be organized temporally by circadian rhythms in response to changes in the environment [16]. Many biological processes are thought to be regulated by melatonin, including circadian rhythm and sleep, metabolic processes, anti-cancer properties and antioxidant effects. Melatonin lengthens the time spent in the REM state, whereas a deficiency in it causes longer NREM periods. Neurodevelopment of the fetus will be disturbed when there is insufficiency in melatonin.

Abnormality in melatonin level is strongly correlated with ASD not only as a symptom, but also as a possible causative factor (Figure 2). Individuals with ASD have altered melatonin secretion patterns that were related to sleep as well as circadian rhythm [17]. As melatonin plays a crucial role in altering the circadian rhythm, it could be speculated that lack of melatonin in children diagnosed with ASD is strongly related their sleep disorder. It is ascertaining that melatonin disruption is associated with neurological and behavioral illnesses like Parkinson's disease and depression, as well as sleep problems like insomnia [17]. Furthermore, melatonin has been shown to enhance dendrite formation and increase the complicity of neurons in the hippocampus in rats [18]. Melatonin is also believed to affect the balance in excitation and inhibition through altering the amounts of neurotransmitters, which is thought to contribute to neurodevelopment. Both dendrite formation deficiency and lack of E/I balance can cause enhancement of autistic behaviors in individual [19].

It can also be speculated that melatonin plays a causative role in prenatal ASD. During pregnancy, Maternal melatonin enters the fetal circulation throughout pregnancy and crosses the placenta, providing the fetus with photoperiodic information. Subsequently, melatonin influences the children's circadian rhythm. As indicated in recent studies, melatonin level in mothers with ASD were lower than the mothers in controlled group [20]. Melatonin insufficiency is hypothesized to be a risk factor in prenatal ASD, since the baby depends on supply of the mother's melatonin through the placenta. Early intervention in those at risk would be taken into account if this suggestion is confirmed by subsequent investigations.

Melatonin is adapted as a common treatment for children with insomnia. Melatonin has been shown in several well-controlled studies to enhance sleep in kids with ASD [21]. Supplementation of melatonin to children with ASD has been revealed as an efficient and secure treatment for disturbance in sleep. The majority of kids improve their sleep latency after receiving a dose of 1 or 3 mg 30 minutes before bed. Improvements in night waking, stereotypical behaviors and anxiety were also reported [22].

Regardless, melatonin is crucial in regulating the circadian system. It is a bidirectional interaction; a system impairment can have a greater influence on the other system. In the light of recent researches, additional melatonin supplemented to individuals with ASD has been warranted as one of the most effective and satisfying treatment for circadian disorder. However, issues such as choosing proper dosage of melatonin still arise. Future studies should consider these issues.

### 4.2. Cortisol

Cortisol increases improves the brain's utilization of glucose and increases the availability of compounds that aid in tissue regeneration. Abnormalities in the rhythm of cortisol has been associated with ASD. Since 1985, children with lower functioning autism were shown to have abnormal rhythmic patterns of cortisol [23]. When compared to younger ASD individuals, researchers discovered that older ASD children had much higher cortisol levels. Additionally, comparing the neurotypical group to the autism children, evening values tended to be consistently elevated. The higher nighttime values may signify a greater receptivity to the day's activities. Interestingly, high levels of cortisol are prevalent in patients with insomnia without depression, especially in the evening and at the start of sleep [23]. Many cases of insomnia are said to have a dysfunctional in the rhythm of cortisol production as their underlying cause. Melatonin levels during pregnancy is crucial to the neuroprotection and the normal development for the baby. Normal melatonin level prevents excessive oxidative stress in the developing fetus's vulnerable brain and regulates sleep cycle of the fetus. Low maternal melatonin level in mothers with ASD elevates the risk of ASD in the fetus. Consequently, once the babies with ASD are born, their lack of melatonin further disrupts sleep and inhibits neural development, exacerbating ASD. Thus, the effect of melatonin in ASD patients are bidirectional.

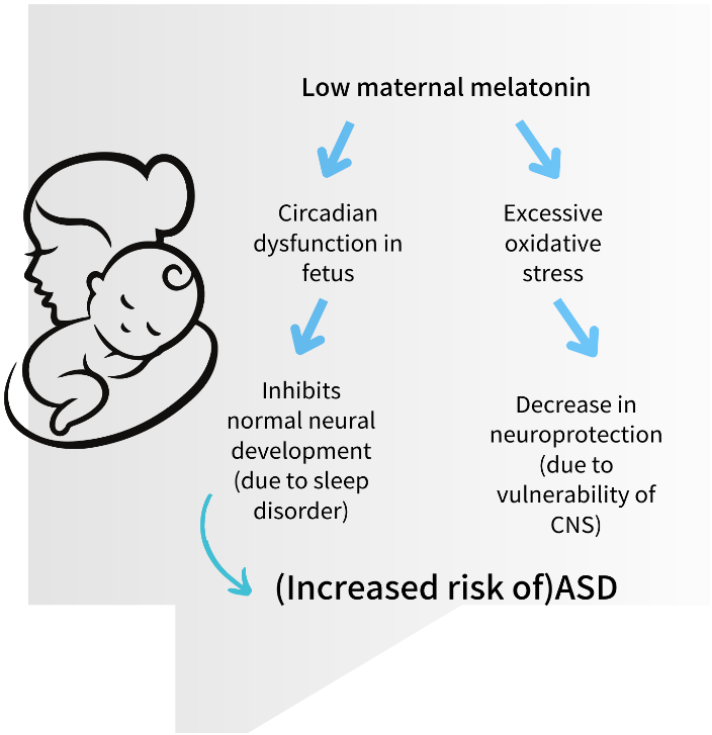



**Figure 2.** The effects of melatonin on development of the fetus.

## 5. Conclusion

Neurodevelopment and child health are receiving a lot more attention as a result of technological advancement and gradual life enrichment. This review summarizes the bidirectional correlation between circadian dysfunction and ASD. A potential strategy to treat ASD may be revealed by recognizing the significance of the circadian clock in it. Children with ASD can benefit from clinical interventions that is a combination mental and social methods. This article propose that it is necessary for future research to warrant and apply the efficacy of circadian rhythm in treatment of ASD and implementing chronotherapy-based treatment plans for the disorders.

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