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Disruption of circadian rhythm and risk of autism spectrum disorder: role of immune-inflammatory, oxidative stress, metabolic and neurotransmitter pathways

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Abstract: Circadian rhythms in most living organisms are regulated by light and synchronized to an endogenous biological clock. The circadian clock machinery is also critically involved in regulating and fine-tuning neurodevelopmental processes. Circadian disruption during embryonic development can impair crucial phases of neurodevelopment. This can contribute to neurodevelopmental disorders like autism spectrum disorder (ASD) in the offspring. Increasing evidence from studies showing abnormalities in sleep and melatonin as well as genetic and epigenetic changes in the core elements of the circadian pathway indicate a pivotal role of circadian disruption in ASD. However, the underlying mechanistic basis through which the circadian pathways influence the risk and progression of ASD are yet to be fully discerned. Well-recognized mechanistic pathways in ASD include altered immune-inflammatory, nitro oxidative stress, neurotransmission and synaptic plasticity, and metabolic pathways. Notably, all these pathways are under the control of the circadian clock. It is thus likely that a disrupted circadian clock will affect the functioning of these pathways. Herein, we highlight the possible mechanisms through which aberrations in the circadian clock might affect immune-inflammatory, nitro-oxidative, metabolic pathways, and neurotransmission, thereby driving the neurobiological sequelae leading to ASD.

Keywords: autism; circadian rhythm; neurodevelopmental; neuro-immune; neurotransmitter; oxidative stress.

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Introduction

Circadian rhythms are the 24 h cycles of biological rhythms involving physiological, mental, and behavioral variations. They are mostly influenced by light and dark stimuli. Circadian rhythms control almost all vital physiological and metabolic processes through the sleep–wake cycle. Endogenous circadian rhythms train and synchronize with environmental cycles. Misaligned environmental cycles and endogenous biological rhythms have deleterious consequences on human health. Multiple studies have demonstrated a link between circadian disruption and adverse mental health outcomes, predominantly mood disorders such as major depressive disorder and bipolar disorder (Lyall et al. 2018; Matson and Nebel-Schwalm 2007; Walker et al. 2020). Besides this, there is an essential role of circadian rhythm in

learning, memory, and cognition (Sahar and Sassone-Corsi 2012a; Schmidt et al. 2007). Studies conducted on Drosophila demonstrated the involvement of circadian genes in potentiating long-term memory (Sakai et al. 2004).

Compelling evidence now suggests important implications of circadian rhythm in neurodevelopment and neuronal functions both during prenatal and postnatal development. Dysregulation of the circadian system could interfere with the crucial phases of brain development and affect neuronal migration, neurogenesis, neurotransmitter signaling, as well as neuronal plasticity (Kobayashi et al. 2015). These abnormalities could influence the manifestation of various neurodevelopmental disorders across different stages of life. Autism spectrum disorder (ASD) is a classical neurodevelopmental disorder having an early onset, as early as 12 months of age. Altered developmental neurogenesis, neurotransmitter signaling, neuroplasticity, and brain morphometry have been proposed to contribute to the neurodevelopmental basis of ASD. Since circadian disruption critically influences these developmental brain processes, there is a possibility that circadian disruption could lead to ASD by driving neurodevelopmental abnormality. There are however few studies showing a direct causal link between circadian disruption and ASD risk. A gene expression study has reported differential expression of 15 circadian rhythm regulatory or responsive genes in severe cases of ASD (Hu et al. 2009). Circadian changes in brain derived neurotrophic factor (BDNF) and its implications for cortical functions in ASD suggest a possible connection between circadian clock and ASD (Katoh-Semba et al. 2007). A link between circadian rhythm and ASD has also been established, based on an increased atypical sleep rhythm, a lower number of rapid eye movements (REMs) during REM sleep, longer sleep latency, and frequent nocturnal awakenings (Limoges et al. 2005). Supported by these sleep studies, the circadian aberration theory is rapidly gaining attention as a risk model of ASD.

ASD is an etiologically complex and phenotypically heterogenous neurodevelopmental disorder. Alongside neurodevelopmental origins, pathways including immune-inflammation, metabolic, oxidative toxicity, and neurotransmitter abnormalities have been linked to ASD pathophysiology. The role of the circadian clock on the functioning of these pathways and the pathobiological implications of their functional interactions in ASD are only beginning to be understood. The disruption of reciprocal interaction among the core components of circadian clock and immune, metabolic, oxidative stress, and neurotransmitter systems might have ramifications on the neurobiological sequelae and symptomatology of ASD. Based on indirect evidences and preliminary understanding, we propose a theoretical model of a circadian disruption-induced aberrant immune-metabolic-oxidative stress-neurotransmitter axis in ASD. Future research and experimental validation of this model will provide important insights into the complex and multifactorial basis of ASD.

Genetic construct of the circadian rhythm

In almost all organisms, the circadian rhythm is modulated by both external (environment) and internal (clock-related genes) factors. The genes involved in the circadian clock homeostasis are well characterized. Circadian rhythms are generated by autoregulatory transcriptional–translational feedback loops (TTFLs), which are driven by core transcriptional activators such as circadian locomotor output cycles kaput (CLOCK), and brain and muscle ARNT-like protein 1 (BMAL1) (Takahashi 2017). CLOCK heterodimerizes with BMAL1 and acts as positive regulator of the loop. The CLOCK-BMAL1 complex binds to enhancer box (E-box) and drives rhythmic expression of the negative regulators, the period (PER1, PER2, and PER3), and cryptochrome (CRY1 and CRY2) proteins. These negative regulators can dimerize themselves to form a homodimer (PER-PER) or heterodimer (PER-CRY). The PER-CRY heterodimer translocates from the cytoplasm to the nucleus and inhibits gene expression induced by CLOCK-BMAL1 (Reppert and Weaver 2002). In addition to the primary CLOCK-BMAL1 feedback loop, there is another regulatory feedback loop which is driven by retinoic acid-related orphan nuclear receptor alpha (RORα) and REV-ERBα. Studies have shown that RORα and REV-ERBα regulate the transcription of BMAL1 through retinoic-acid-related orphan receptor elements (ROREs) (Guillaumond et al. 2005). ROREs activate the transcription of BMAL1, whereas REV-ERBs suppress the transcription of BMAL1 and also repress transcription of CLOCK and CRY1 genes (Preitner et al. 2002). The period, phase, and amplitude of circadian rhythm are influenced by circadian gene variants and entrained by environmental factors such as exposure to light, social cues, mealtimes, and work schedules.

Under normal circumstances, people exhibit various circadian phenotypes or chronotypes. These chronotypes are influenced by an individual's genetic background as well as environmental cues. Notably, genetic variations have been reported in several clock-related genes in the general population (Ciarleglio et al. 2008). Some of the

variants of the clock genes are significantly associated with the chronotype, like morningness (Jones et al. 2016). There is an association of genetic or polymorphic variants of circadian genes with a range of neuropsychiatric, metabolic, malignant, and cardiovascular disorders (Jagannath et al. 2017). A list of genes and their implications on circadian rhythm are summarized in Table 1.

Molecular clock and its cellular drivers: implications in neurobiology

The molecular mechanisms controlling circadian rhythms are relatively well understood. Circadian rhythmicity is regulated by a master clock in the suprachiasmatic nucleus (SCN) located in the hypothalamus. The SCN is the main center that directs circadian rhythms in the body by regulating daily cycles of physiology and behavior. Studies linking SCN to the circadian rhythm were first published as early as 1972. In this study, the primary and accessory optic tracts in rats with lesions in the SCN were not sufficient to maintain the corticosterone rhythm (Moore and Eichler 1972). Damage in the SCN also modified the drinking and locomotory behavior of rats. This suggested that the SCN may contain pacemakers crucial to maintain normal circadian rhythms (Stephan and Zucker 1972). Subsequently, the SCN was established as the circadian oscillator in the brain, based on the fact that circadian rhythmicity did not exist in any part of the brain when connections to the SCN were cut using a Halasz knife (Inouye and Kawamura 1979). These and other landmark studies indicated the ability of SCN to divulge rhythmicity to other parts of the brain (Weaver 1998). Neurotransmitters profoundly influence the functioning of the SCN. For example, *Gamma*-aminobutyric acid (GABA) expression in the SCN was necessary for refining circadian output rhythm in mice (Ono et al. 2019). Circadian genes like PER2 are expressed mainly in the SCN and other brain areas, including the midbrain and forebrain as well as the peripheral nervous system. Circadian rhythm-related genes are differentially expressed in these brain regions, and their expression follows diurnal patterns (Staehle et al. 2020). In addition to the SCN, there are numerous other cellular clocks in tissues across the body and the SCN coordinates with these cellular clocks. The SCN executes this coordination through circadian control of various signals, such as autonomic, neuroendocrine, and behavioral that entrain cellular clocks across diverse tissues (Mohawk et al. 2012). There are cell-autonomous clocks inside the brain. Circadian TTFLs in neurons and astrocytes can drive molecular oscillations in the SCN and circadian behavior in mice. The astrocytic clock regulates the circadian function of SCN neurons via glutamatergic signals and by regulating expression of clock genes (Brancaccio et al. 2019). Key clock genes have widespread expression in the brain (Abraham et al. 2005) and have an essential role in many brain functions. BMAL1 is involved in hippocampal and astrocytic function (Jilg et al. 2010; Marpegan et al. 2011). BMAL1 deletion in mice led to impairments in learning and memory (Kondratova et al. 2010). More importantly, a recent study on mice has established that BMAL1 deletion and its reduced expression promoted neuronal cell death by regulating neuronal redox homeostasis; implying a critical role of impaired

Table 1: Mammalian genes regulating circadian rhythm and the effect of their mutations.

Genes	Functions	Effect of mutations
CLOCK	It is a transcription factor. It binds to BMAL1 and is involved in a positive feedback loop. It promotes transcription of PER and CRY genes.	Circadian rhythm is affected but not completely abolished.
BMAL1	It is a transcriptional activator. Binds with CLOCK to form a positive feedback loop. The heterodimer interacts with E-box elements upstream of Period gene.	Formation of the heterodimer is severely affected.
Period (PER1, PER2, and PER3)	It associates with CRY gene product to form a heterodimer. Negatively regulates the production of Clock protein. These are CLOCK-BMAL1 inhibitors.	Mutations in PER genes lead to sleep disorders and also reduce the duration of the rhythm.
Cryptochrome (CRY1 and CRY2)	Dimerizes with PER and stabilizes its protein products. They act as CLOCK-BMAL1 inhibitors.	Reduces free-running periodicity and locomotor activity in mammals.
REV-ERBα	Negative regulator of BMAL1 transcription. Regulated by PER gene transcription.	It severely affects BMAL1 transcription.
RORα	Positive regulator of BMAL1. Competes with REV-EBB (α, β) for binding with ROREs which in turn regulate transcription of BMAL1.	Mutations have been shown to affect the transcription of BMAL1 and CRY1.

clock genes in neurodegeneration (Musiek et al. 2013). PER2 also has a significant impact on various neurobiological activities, including sleep, depression and addiction (Kim et al. 2018).

The circadian system modulates multiple functions of the brain such as autonomic nervous system (ANS) balance, and the central nervous system (CNS)/ANS interactions (Buijs et al. 2013; Riganello et al. 2019). The components of the circadian rhythm play pivotal roles in the regulation of neurodevelopment, neurotransmission, neuronal plasticity, sleep, and learning and memory. Therefore, circadian rhythms potentially regulate multiple core neurophysiological processes that are relevant to behavior. Aberrations in circadian rhythm and the consequent neurobiological processes may drive various brain disorders across the lifespan (Logan and McClung 2019). For example, dysregulation of neurotransmitters like dopamine by circadian clock components has profound impacts on mood and addiction (Hampp et al. 2008; Kim et al. 2017; Parekh et al. 2015).

Circadian dysregulation in ASD: a review of evidence

The first indication that the circadian rhythm might be affected in ASD was reported almost 50 years ago when Ritvo et al. observed an abnormal increase in serotonin levels in the blood of autistic individuals compared with age-matched controls (Ritvo et al. 1970). Subsequently, many studies highlighted the relevance of circadian disruption in the risk and progression of ASD. Genetic studies have provided important insights into the role of genetic determinants of the circadian clock in the risk ASD. Considerable genetic variation exists within the coding region of human circadian rhythm genes such as PER1, PER2, PER3, Aryl hydrocarbon receptor nuclear translocator-like protein 1(ARNTL), CRY2, CLOCK, and TIMELESS (Hawkins et al. 2008). Converging evidence suggests that CLOCK genes play an important role in ASD (Wimpory et al. 2002). Contextually, circadian genes are highly polymorphic in ASD (Yang et al. 2016). In a study on single nucleotide polymorphisms (SNPs) of 11 CLOCK/CLOCK-related genes, PER1 and neuronal PAS domain protein 2 (NPAS2) were significantly associated with ASD (Nicholas et al. 2007). The possible association between circadian abnormality and the risk of ASD has been discussed in the following sections.

Altered sleep–wake cycle and disrupted melatonin biosynthesis

Sleep disturbance and circadian sleep alterations are common or the most frequently associated comorbid condition in children with ASD. Multiple factors seem to drive the sleep disturbances in people with ASD (Glickman 2010; Rana et al. 2021). Circadian sleep dysrhythmicity may predispose children to ASD symptoms (Carmassi et al. 2019). Neonatal abnormal sleep–wake rhythm may be a predictor of future development of ASD (Miike et al. 2020). Sleep disturbances may precede and worsen the behavioral outcomes in children with ASD. For example, disturbances in continuous sleep and circadian rhythms have been linked to behavioral difficulties such as high irritability as well as high stereotypic behaviors in children with ASD (Yavuz-Kodat et al. 2020). Autistic traits in toddlers were recently associated with sleep problems, particularly daytime sleepiness (Horiuchi et al. 2020). REM sleep has been postulated as an index of brain plasticity (Elia et al. 2000). Impaired REM sleep can thus be considered as a marker of abnormal brain functioning. Contextually, persistent sleep disturbance was associated with neuronal damage and impaired brain development (Jan et al. 2010; MacDuffie et al. 2020). A correlation between altered subcortical brain volumes and sleep onset problems in first two years of life may predispose infants to ASD; this further implies the neurodevelopmental connection of sleep abnormality in children with ASD (MacDuffie et al. 2020). Interestingly, genes regulating the circadian rhythm also affect sleep behavior (Patke et al. 2017). SHANK3, a candidate gene of ASD modulates sleep as well as the expression of the circadian transcription factors like PER3, Bhlhe41, Hlf, Tef, and Nr1d1 in mouse (Ingiosi et al. 2019). Thus, sleep can be considered as a translationally-relevant endpoint in ASD pathobiology and therapeutics (Missig et al. 2020).

Melatonin is involved in an arsenal of pathways in the human body; foremost among them is the regulation of the circadian rhythm and sleep–wake cycle (Cajochen et al. 2003). Melatonin has neuroprotective effects and it is essential for normal neurodevelopment (Jin et al. 2018). Studies on rodent hippocampus have shown that fluctuating melatonin levels have a significant effect on synaptic plasticity (Hogan et al. 2001), and long-term potentiation in the hippocampus (Wang et al. 2005). Hippocampal dysfunction, as well as altered synaptic plasticity, is implicated in ASD (Dager et al. 2007; Guang et al. 2018;

Schumann et al. 2004). Many studies point towards abnormal melatonin synthesis in ASD (Melke et al. 2008; Wu et al. 2020). There have been many reports of decreased night time melatonin levels in autistic children. This is correlated with the physiological abnormalities including sleep onset latency, lower total sleep time in patients with autism (Limoges et al. 2005), and lower REM sleep (Buckley et al. 2010). Genetic studies have also supported a role of melatonin in ASD. Acetylserotonin O-methyltransferase (ASMT) is the last enzyme of the melatonin synthesis pathway. Splice site mutation in ASMT (*IVS5+2T>C*) is associated with ASD, indicating a potential involvement of this gene in ASD (Jonsson et al. 2010). Genetic variations within the melatonin receptor (MTNR1N and MTNR1B) genes were also reported in ASD (Chaste et al. 2010). The genetic variants within the melatonin pathway enzymes, ASMT and cytochrome P450 1A2 (CYP1A2) were also associated with sleep onset delay in ASD (Veatch et al. 2015).

Altered activity of the hypothalamic–pituitary–adrenal (HPA) axis

The hypothalamic–pituitary–adrenal (HPA) axis and the circadian clock system regulate each other's activity at multiple levels (Nader et al. 2010). The HPA axis is crucially involved in stress responsivity. This is mediated by the release of glucocorticoid hormones from the adrenal cortex. Cortisol (hydrocortisone) is the primary glucocorticoid in humans. Cortisol shows pronounced diurnal variations, peaking in the early morning and reaching its lowest level in the evening (Pruessner et al. 1997; Weitzman et al. 1971). A dysfunctional HPA axis and altered levels of cortisol are reported in the blood, serum, and saliva of patients with ASD and are also shown to influence the severity of ASD (Curin et al. 2003; Lakshmi Priya et al. 2013; Spratt et al. 2012; Tordjman et al. 2014). Changes in cortisol circadian rhythms have been reported, in the children with ASD, with lower cortisol levels in the morning and higher levels in the evening (Corbett et al. 2008).

Circadian disruption and risk of ASD: possible underlying mechanisms

Disruption of circadian rhythms may lead to desynchronization of several physiological processes. This includes augmented inflammatory activity and diminished immunological defenses, aberrant functioning of neuroendocrine stress responses, excessive generation of reactive oxygen species (ROS), disrupted neurotransmission, and synaptic plasticity. All these changes have pathobiological relevance in ASD. The implications of circadian disruption on these pathways and their possible impact on ASD risk are discussed in the following sections and summarized in Figure 1.

Circadian rhythm, development, and ASD risk

Converging findings in offsprings suggest an association between early neurodevelopmental abnormalities and risk of ASD (Livingston and Happe 2017; Xiao et al. 2014). The core elements of the circadian clock regulate brain development. PER3 is a critical component of the circadian clock and its expression has been reported in mouse cerebral cortex during embryonic to postnatal development. PER3 is crucial in regulating corticogenesis, and PER3 deficiency affects neuronal migration in the developing brain (Noda et al. 2019). In addition to this, another circadian gene, Nr1d1 (Nuclear receptor subfamily 1 group D member 1), also known as REV-ERBα plays an important role in the regulation of excitatory neuron migration and synaptic network formation (Goto et al. 2017). Subsequent to this, other studies

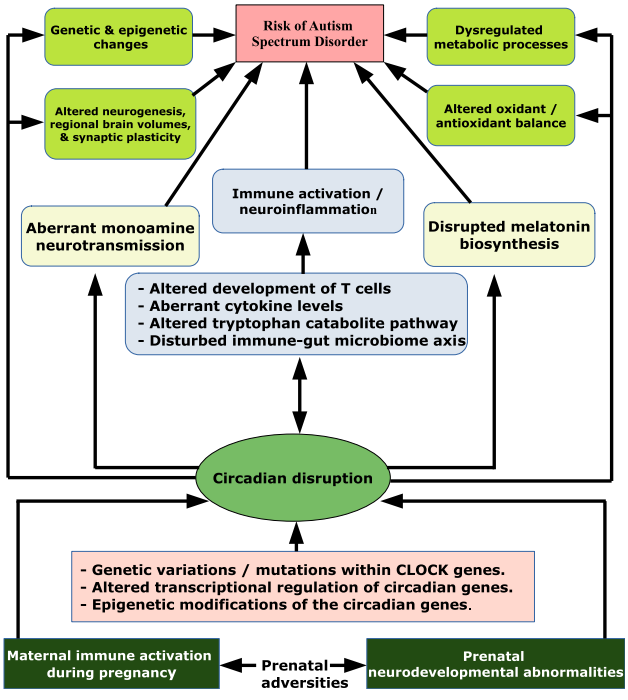

Figure 1: Summarizes the possible impact of circadian disruption on the risk of autism spectrum disorder by inducing changes in various cellular and molecular pathways.

also supported a developmental role of circadian genes (Kobayashi et al. 2015). The circadian genes determine the critical period timing of various neuronal processes like neuronal migration, neurogenesis as well as neuronal plasticity both during prenatal and postnatal brain development. A recent mouse study suggests that early-life disruption of circadian rhythm results in long-lasting changes in somatic and behavioral development (Smarr et al. 2017). Notably, the programming of neurobiological changes relevant to ASD pathophysiology also occurs during prenatal as well as postnatal brain development. Support towards a link between circadian induced neurodevelopmental abnormality and risk of ASD has also been derived from genetic studies. Mutations/genetic variations within both the circadian genes, PER3 and Nr1d1 involved in neurodevelopment were reported in patients with ASD (Goto et al. 2017; Yang et al. 2016).

Circadian rhythm, immune dysregulation, and ASD risk

Close interactions and reciprocal regulation of circadian rhythm and immune function exist. This is essential in maintaining physiological homeostasis, neuronal function, and behavior (Cermakian et al. 2013). Disruption of the cross-talk between circadian clock elements and the immune components might have enduring effects on neuronal processes as well as behavior. This section will highlight the bidirectional cross-talk between circadian rhythms and the immune system and the possible deleterious consequences of altered regulation of these biological processes on the risk and progression of ASD.

Cells of the immune system have molecular clock components. Clock genes are present within macrophages, dendritic cells, and B and T lymphocytes (Bollinger et al. 2011; Silver et al. 2012). It is noteworthy that some circadian proteins are involved in the differentiation and lineage commitment of T lymphocytes. For example, RORγ or RORα have direct regulatory roles in the circadian expression of clock genes (Takeda et al. 2012). Mice deficient of RORγ or RORα have significantly reduced expression levels of CRY1, BMAL1, E4bp4, REV-ERBα, and PER2. Lack of RORα or RORc impairs development of Th17 cells (Yang et al. 2008). These and other findings suggest a critical role of RORs in the circadian rhythm, immunity, and metabolism (Jetten 2009).

Circulating immune cells, levels of cytokines and chemokines as well as expression of adhesion molecules involved in the migration of immune cells exhibit 24 h daily oscillations (Labrecque and Cermakian 2015; Nakao 2014). Homing of lymphocytes to lymph nodes generally peaks at night, and they exit the tissue during the day. This implies circadian regulation of lymphocyte trafficking through lymph nodes (Druzd et al. 2017). There is a growing recognition that diurnal variation of the immune response is also promoted by microglia, the resident immune cells in the brain (Martinez-Tapia et al. 2020). Microglia too possesses a circadian clock, and microglia-mediated neuroinflammatory responses are controlled by this circadian clock (Fonken et al. 2015).

Circadian rhythms also influence the efficiency of the immune response, although the precise mechanistic basis is yet to be fully elucidated. This could be achieved through molecular interactions between the regulators of circadian rhythm and the immune system. The mediators of the circadian clock have a direct effect on transcriptional activity of the immune components, driving the expression or repression of immune genes (Hergenhan et al. 2020).

Possible mechanisms

Aberrant immune responses, inflammation, and autoimmunity are linked to ASD (Meltzer and Van de Water 2017). Among the immunological abnormalities in ASD, systemic inflammation indexed by elevated levels of inflammatory cytokines, such as TNF-α, IFN-γ, IL-1β, IL-8, and IL-17 as well as a disrupted T cell network and neuroinflammation are common (Ashwood et al. 2011; Masi et al. 2015). Chronic disruption of the circadian rhythm contributes to inflammatory responses (Castanon-Cervantes et al. 2010). In mice, long-term circadian misalignment accelerates immune senescence as well as chronic inflammation (Inokawa et al. 2020). It is envisaged that immune abnormalities and/or inflammation in ASD could be the result of circadian dysregulation. Though empirical support for this notion is currently not available, indirect evidences explicated below does not rule out such a possibility.

i) Th17 cells are increasingly being implicated in the immune-inflammatory responses. Higher number of activated Th17 cells are reported in children with ASD (Basheer et al. 2018). Another study examining Th17/Treg cells imbalance observed a significantly skewed response towards Th17 in children with ASD (Moaaz et al. 2019). Reduced expression of RORα, a master regulator of Th17 cells was reported in brains of individuals with ASD and this was influenced by epigenetic alterations in the RORA gene (Nguyen et al. 2010). RORα is directly involved in the regulation of circadian expression of clock genes. A deficit in RORα activity would affect circadian rhythm and

also Th17-pathway driven immune-inflammatory responses.

ii) Maternal immune activation (MIA) due to prenatal environmental adversities enhances neurodevelopmental aberrations and ASD-like behaviors in offspring (Lombardo et al. 2018). Interestingly, a recent study on MIA in mice demonstrated a link between circadian disruption and neurodevelopmental disorder (Delorme et al. 2021). These findings suggest a possible impact of prenatal circadian disruption on ASD-risk in the offspring and also indicate the possibility of direct detrimental effects of a disrupted circadian rhythm during prenatal development on immunological sequelae and risk to ASD in offspring,

iii) Another possible mechanism through which circadian rhythm could alter immune functioning is through alteration of the gut microbiota. Dysregulated circadian rhythm has long-lasting effects on gut microbiota (Voigt et al. 2014). Interestingly, disturbances in the gut microbiome have also been associated with insomnia and circadian misalignment (Parkar et al. 2019; Pietruczuk et al. 2018). Diurnal oscillations of composition and function of gut microbiota have been reported. This has a substantial impact on metabolic homeostasis and such diurnal variation of microbiota influences the host's circadian transcriptional as well as epigenetic oscillations. A recent study shows that altered microbiome rhythmicity has a deleterious impact on normal chromatin and transcriptional oscillations and may also drive genome-wide *de novo* oscillations (Thaiss et al. 2016).

Gut microbiota play pivotal roles in immune homeostasis (Wu and Wu 2012). A dysregulated gut microbiome may fuel inflammation, including neuroinflammation and also accelerate immune senescence (Hakansson and Molin 2011). Such dysregulation has a profound impact on host physiology and may also increase susceptibility to diseases, including neuropsychiatric illnesses (Nobs et al. 2019; Petra et al. 2015). Contextually, gut microbiota alterations are increasingly being associated with ASD in recent times (Dan et al. 2020; Ding et al. 2020). Thus, circadian clock through modulation of gut microbiota might dysregulate immune responses in ASD.

Circadian rhythm, activation of oxidative stress pathway, and ASD risk

Circadian rhythms and stress-regulatory pathways are intimately involved in various physiological and signaling processes (Stangherlin and Reddy 2013). Under stressful conditions, the stress-regulatory system fails to maintain balance between oxidants and anti oxidants and also alters circadian timing processes. Impaired circadian rhythm and oxidative stress pathways exert a number of adverse effects at cellular and organismal levels. Disrupted circadian rhythms and activated oxidative stress pathways alter neuronal processes as well as behaviors. This section is aimed at discussing the functional interplay between circadian rhythms and stress-regulatory pathways and its possible implications on ASD pathophysiology.

Oxidative stress toxicity reflects an imbalance between oxidative stress and antioxidant defenses due to either excessive formation of ROS, such as superoxide radicals (O_2-), peroxides (ROOR), and hydroxyl radicals (OH-), or disrupted redox defenses. A considerable body of evidence now suggests that circadian rhythms have a significant impact on the oxidative stress defense system (Wilking et al. 2013). A circadian variation of the mediators of oxidative stress pathway and rhythmic changes in oxidative damage to DNA, protein, and lipid molecules have been demonstrated (Hardeland et al. 2003). CIRCADIAN CLOCK ASSOCIATED 1 (CCA1) acts as the master regulator of ROS homeostasis and plays a critical role in ROS mediated oxidative stress responses (Lai et al. 2012). Also, several key enzymes and antioxidants such as superoxide dismutase (SOD), catalase (CAT), peroxiredoxins (Prx), glutathione peroxidase (GPx), glutathione disulfide (GSSG), glutathione reductase (GR), and glutathione S-reductase (GST), known to protect against free radicals oscillate with circadian rhythmicity (Xu et al. 2012). An intricate connection exists between abnormal sleep rhythms and ROS generation (Blanco et al. 2007; Kanabrocki et al. 2002). A recent study reported higher levels of oxidative stress damage and lower levels of antioxidant responses in night shift workers compared to day workers (Teixeira et al. 2019).

Genes regulating oxidative stress are also influenced by circadian clock. Syrian hamsters exposed to continuous light for two weeks had diminished expression of antioxidants like SOD, CAT, and GR compared to controls (Tomas-Zapico et al. 2003). Knockout studies of PER gene in mice showed that the production of SOD1 was linked to the circadian rhythm and that rhythmicity was abolished in PER knockout mice (Jang et al. 2011). Mutations in the PER, REV-ERBα, CLOCK, or BMAL1 genes were shown to alter the production of antioxidants in the body significantly.

It is now evident that oxidative stress pathways are activated in ASD (Bjorklund et al. 2020a). Several oxidative stress markers such as cysteine, total glutathione, free reduced glutathione and cystathionine, and oxidized

disulfide form of glutathione are altered in blood as well as urine in ASD (Bjorklund et al. 2020b; Osredkar et al. 2019). Defective antioxidant defense mechanisms due to lowered levels of SOD and glutathione peroxidase (GSH-Px) and increased malondialdehyde (MDA), a marker of lipid peroxidation was observed in ASD patients (Meguid et al. 2011). ASD patients also have dysfunctional Nrf2 regulation resulting in increased nitrosative stress (Nadeem et al. 2020). Increased mitochondrial dysfunction and damage to mitochondrial DNA are evident in ASD patients (Griffiths and Levy 2017; Napoli et al. 2013; Rossignol and Frye 2014). Disruption of electron transport chain (ETC) leading to ROS generation has been observed in patients with ASD (Chauhan et al. 2011). Interestingly, all these processes seem to be controlled in part or in full by circadian rhythms. Although a few data directly link circadian disruption with altered oxidative stress pathway in ASD, a study has demonstrated regulatory role of core circadian proteins in neuronal redox homeostasis and linked impaired function of the clock genes to neurodegeneration (Musiek et al. 2013). Based on these data, a disrupted circadian rhythm is likely to be involved in driving ASD pathogenesis, at least in part through induction of oxidative stress pathway.

Circadian rhythm, metabolic abnormalities, and risk of ASD

Circadian rhythms strongly influence metabolic processes and show a bidirectional cross-talk with almost all metabolic processes, such as carbohydrate, lipid, protein, and amino acid metabolism (Serin and Acar Tek 2019). Circadian rhythms regulate the overall metabolic homeostasis by interacting with metabolic processes both at the neuroendocrine and neuroanatomic levels. Chronic disruption of circadian rhythm leads to significant changes in metabolism and subsequently to neuronal plasticity and behavior (Karatsoreos et al. 2011). In this section, we highlight the functional interactions between circadian and metabolic pathways and their possible implications in ASD pathobiology.

Circadian rhythms are involved in the metabolism of glutathione and many other metabolites. Dramatic oscillations in glucose, lipid, protein, and amino acid metabolism occur at different times of the day. Methionine, a vital amino acid shows circadian variation. It is also essential for the conversion of serotonin to melatonin in the dark and is catalyzed by N-acetyltransferase (NAT). During the dark hours, norepinephrine release is upregulated from the nerve endings of the superior cervical ganglion. This results in increased levels of cAMP in pinealocytes that produce more melatonin. The rhythmic expression and activation of metabolic pathways take place in coordination with clock genes, such as BMAL1, PER2, PER3, CRY1, and CRY2 (Sahar and Sassone-Corsi 2012b). Interestingly, rhythmicity of homocysteine levels has also been demonstrated to be dependent on CLOCK (Paul et al. 2014).

Possible mechanisms

Compelling evidence suggests important implications of metabolic abnormalities in ASD pathobiology (Cheng et al. 2017; Frye et al. 2013). Elements like homocysteine, glutathione, tryptophan, cysteine, creatinine, and neurotransmitters such as serotonin, melatonin, and norepinephrine are altered in ASD (Delaye et al. 2018; Rose et al. 2012; Wang et al. 2016). Dysregulated circadian rhythm is likely to alter metabolism in brain and contribute to ASD. Although a direct causal link has not yet been established by empirical studies, one of the possible mechanisms through which circadian-metabolic axis might drive neurobiological basis of ASD is by modulating the tryptophan catabolite (TRYCAT) pathway.

Tryptophan metabolism follows a circadian pattern (Rapoport and Beisel 1968). Tryptophan catabolism through kynurenine pathway is crucially involved in inflammation. An aberrant TRYCAT pathway has been linked to ASD by several studies (Boccuto et al. 2013; Kaluzna-Czaplinska et al. 2017). Alterations in the circadian rhythms due to tryptophan metabolism or *vice versa* and their modulatory effects on inflammation might influence ASD pathobiology.

Circadian rhythm, disrupted neurotransmission, and ASD risk

Circadian rhythms regulate the release and function of multiple neurochemicals. Equally, various neurotransmitters also modulate circadian rhythms. The expression of neurotransmitter-related genes in different brain regions also follows circadian patterns (Weber et al. 2004). Circadian rhythms regulate neural systems such as limbic brain regions and monoamine neurotransmitters associated with behavioral abnormalities. Disruption of circadian rhythm has enduring effects on neuronal signaling. This might have significant impact on neurobiological activities as well as behavior. In this section, the relevance of cross-talk between circadian rhythm and neurotransmitters and the possible impact of a disrupted cross-talk between these

systems on the risk and progression of ASD will be discussed.

It is now evident that monoamine neurotransmitters serve as modulators of circadian rhythm in the CNS. Several studies have conclusively shown serotonergic modulation of circadian rhythmicity (Morin 1999). Loss of serotonergic neurons leads to the earlier onset and late offset of nocturnal activity and increased sensitivity of circadian rhythm to light (Morin 1999). Monoamine neurotransmitters are also shown to mediate circadian-induced alterations in mood and behavior (Kim et al. 2017). In a study on rats, circadian disruption was shown to influence the levels of neurotransmitters and behavior. Rats with circadian rhythm disruption had decreased levels of serotonin and showed anxious behaviors (Matsumura et al. 2015).

Circadian control of dopaminergic activity and modulatory effects of dopamine in maintaining proper circadian rhythmicity in different brain areas by influencing clock genes and proteins is widely recognized (Korshunov et al. 2017). Diurnal variations exist in the levels of dopamine transporter (DAT), tyrosine hydroxylase (TH) in the medial prefrontal cortex, nucleus accumbens, and caudate, and these changes are dependent on SCN regulation (Sleipness et al. 2007). The concentrations of dopamine, glutamate and GABA in the rat nucleus accumbens show circadian rhythms (Castaneda et al. 2004). An altered dopamine circuit due to circadian disruption has implications in behavioral abnormalities and psychopathology (Verwey et al. 2016). Knockdown of the CLOCK gene in the ventral tegmental area (VTA) of mice led to increased dopaminergic activity and resulted in manic episodes (Mukherjee et al. 2010). Mice with a CLOCK mutation had increased dopaminergic activity in the VTA, and this was associated with mania-like behavior: however, behavioral abnormalities were rescued by expressing a functional CLOCK protein in the VTA (Roybal et al. 2007).

Possible mechanisms

Several independent lines of research support the hypothesis that dysfunctional neurotransmitter systems are involved in the etiology of ASD (Chugani 2012). The monoamine neurotransmitters such as GABA, serotonin, dopamine, and glutamate have long been implicated in ASD pathogenesis (DiCarlo et al. 2019; Hamilton et al. 2013; Horder et al. 2018). Though a direct causal link is yet to be established, multiple studies indicate a possible role of chronic circadian disruption in inducing neurochemical and neuroplasticity changes in ASD. Such evidences include:

i) Serotonin is a precursor of melatonin and dysregulations of serotonin can cause abnormal production of melatonin. Hyperserotonemia leads to a lowered production of melatonin which in turn causes disturbances in the circadian rhythm. Some studies reported that almost one-third of ASD patients have hyperserotonemia (Croonenberghs et al. 2007; Kolevzon et al. 2010).

Developmental disruption of the serotonin systems alters circadian rhythms (Paulus and Mintz 2012). Disruptions of serotonin signaling during early brain development might be involved in ASD (Yang et al. 2014). Thus, developmental dysregulations of serotonin systems and circadian clock might be linked to ASD risk.

ii) A possible functional interaction between synaptic and clock genes has been proposed in the risk of ASD (Bourgeron 2007). It is noteworthy that synaptic plasticity also varies with a 24-h rhythm. Disruption of circadian rhythm affects synaptic plasticity. It is becoming increasingly apparent that the clock machinery in the brain controls the genes of synaptic components like neuropeptides, neurotransmitter regulators, receptors and transporters, ion channels, vesicle proteins, adhesion and scaffolding proteins, implying that the clock machinery influences synaptic plasticity through transcriptional control (Hannou et al. 2020).

Epigenetic influence on circadian rhythmicity and ASD

Epigenetic processes such as DNA methylation, histone modification and noncoding RNA, like microRNA (miRNA) alterations respond promptly to environmental changes. Interestingly, rhythmicity in epigenetic events is evident in cells and tissues. The circadian system also has a significant influence on many epigenetic regulators. Epigenetic processes also have robust impacts on sleep patterns. Lack of sleep only for a single night alters both DNA methylation and the transcriptional profile of key circadian genes (Cedernaes et al. 2015). Altered DNA methylation seems to influence susceptibility to autism (Tremblay and Jiang 2019).

Sleep loss has a profound impact on epigenetic modifications of circadian genes. This can confer risk to ASD and may influence the severity of ASD. Besides DNA methylation, miRNAs, the endogenous single-stranded, noncoding RNA molecules regulate gene expression negatively and post transcriptionally. miRNAs are involved

in the development and function of the nervous system (Nguyen et al. 2018; Olde Loohuis et al. 2012). miRNAs have emerged as key elements in circadian clock regulation in recent times. Two miRNAs (miR-219 and miR-132) specific to the brain influence circadian timing processes (Cheng et al. 2007). Notably, these two miRNAs are significantly down-regulated in children with ASD (Sarachana et al. 2010). Besides this, recent studies also identified mRNA targets of ASD-associated miRNAs showing enrichment for circadian-related pathways (Hicks et al. 2020; Huang et al. 2015).

Gut microbiota plays an important role in epigenetic processes by producing low molecular weight substances, such as folate, butyrate, biotin, and acetate. Altered gut microbiota and low levels of butyrate were reported in children with ASD (Liu et al. 2019). In an animal model study, sodium butyrate was shown to attenuate social behavior deficits and modify the transcriptional activity of inhibitory/excitatory genes (Kratsman et al. 2016). These findings point towards important role of epigenetic processes of circadian elements in ASD pathophysiology.

Impact of circadian disruption on predominant etiological models of ASD: *Quo vadis*?

There is an increasing interest in the role of the circadian rhythm in the regulation of the immune system. As alterations in immune function/activity are an integral aspect of the etiology and pathophysiology of ASD, it would be interesting to discern how pineal melatonin may be acting via BMAL1, to inhibit pyruvate dehydrogenase kinase (PDK), thereby disinhibiting the pyruvate dehydrogenase complex (PDC), leading to an increased conversion of pyruvate to acetyl-CoA (Anderson et al. 2019). Acetyl-CoA increases ATP from the tricarboxylic acid (TCA) cycle and oxidative phosphorylation as well as serves as a necessary co-substrate for the mitochondrial and cytoplasmic melatonergic pathway (Gevezova et al. 2020). It is by such processes that the circadian rhythm 'resets' immune cells and leads to their optimal daytime functioning. Pineal melatonin may also have similar effects on other cell types. As alterations in mitochondrial and immune cell functions are important aspects of ASD pathophysiology, it is important to note the interface of the circadian rhythm with metabolism. Data obtained from studies conducted on platelets, intestinal epithelial cells and the pineal gland indicate that melatonin may be suppressed in many body cells, at least in part via an increase in microRNAs that suppress the melatonergic pathway (Maes et al. 2019; Pagan et al. 2017). Besides suppression of pineal melatonin production, local melatonin production in different cells, including within the immune cells is also modulated by circadian rhythms. This is an important area for further investigation as it links circadian dysregulation with metabolism, and thereby alters the regulation of the immune response. This has etiological (Seo and Anderson 2019), as well as pathophysiological implications (Anderson and Betancort Medina 2019). Such processes also overlap with alterations in the gut microbiome, which, as noted, are common in ASD. It would be interesting to note that the decrease in the short-chain fatty acid, butyrate, in ASD may be intimately linked to alterations in circadian gene, mitochondrial, immune and melatonergic pathway functions (Jin et al. 2016; Maes et al. 2019). Microbiome derived butyrate increases the melatonergic pathway (Jin et al. 2016), as well as optimizes mitochondrial function, partly by acting via BMAL1 and PDC disinhibition, thereby optimizing mitochondrial oxidative phosphorylation and immune cell function (Maes et al. 2019). Changes in the gut microbiome are therefore important to the regulation of the immune response as well as wider effects via the regulation of metabolism (Anderson and Maes 2020).

Circadian pathway: a potential target of therapy

Many studies both in animals as well as in humans have convincingly demonstrated that the pharmacological modulators of the circadian clock could emerge as potential therapeutic drugs in diseases where circadian disruption plays a critical pathogenetic role (Antoch and Kondratov 2013). Recent reports suggest that circadian genes could serve as potential therapeutic targets in various pathologies, including cancers (Elshazley et al. 2012). Circadian elements could also be considered as important targets of therapy in ASD. Primary evidence towards this has been garnered from studies on melatonin mediated sleep regulation in children with ASD. Given its roles in neurodevelopment, circadian entrainment and sleep regulation as well as in ASD risk, melatonin supplementation is a putative treatment option for sleep disorders in children with ASD (Lalanne et al. 2021). Melatonin supplementation has shown promising results in treating sleep onset insomnia in children with ASD (Malow et al. 2012, 2021).

Conclusion

Disrupted circadian rhythm might induce neurodevelopmental changes and drive the pathogenetic pathways of ASD. Dysregulation of several circadian components has also been reported to influence many processes such as brain development, synaptic plasticity, and cognitive skills, which are altered in ASD. But how circadian rhythms impact the developmental pathology in ASD remains enigmatic. From the fragmented observations and individual studies, it is evident that alterations in circadian rhythm can impact neurodevelopment as well as immune-inflammatory, metabolic, nitro-oxidative stress, and neurotransmitter pathways. This could be either through epistatic interactions or epigenetic modifications. Future research in ASD should focus on understanding the impact of disruption in circadian rhythm on neurodevelopment by integrating all these immune-inflammatory, metabolic, nitro oxidative stress, and neurotransmitter pathways to more precisely understand the interactions between circadian rhythm and the pathophysiological pathways of ASD and to delineate new drug targets to treat patients with ASD.

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