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Melatonin and Circadian Rhythm in Autism Spectrum Disorders

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SUMMARY

Objective: Autism spectrum disorders (ASD) are neurodevelopmental disorders of early childhood which are characterized by limited social-emotional reciprocity and restricted, repetitive patterns of interest and behaviors. The pathophysiology of ASD has not been fully elucidated. Dysregulation of circadian rhythm and melatonin might play a role in ASD pathogenesis. This article aims to review the relationship between melatonin, circadian rhythm and ASD in detail.

Method: Articles published in the PubMed database between 1990-2019 were reviewed and prominent studies in the scope of the review were included.

Results: Decreased melatonin levels were detected frequently in ASD and melatonin replacement treatment for sleep disorders accompanying ASD has given satisfactory results. Similarly, circadian rhythm disorders were frequently reported in ASD, which might increase the susceptibility to ASD through their effects on synaptic plasticity in the early neurodevelopment. Mutations in the clock-controlled genes were also common in ASD.

Conclusion: Further are required for understanding the relationship between melatonin, circadian rhythm and ASD, which will not only shed light on the role of melatonin in the etiology of ASD, but may also guide to early intervention options.

Keywords: Melatonin, circadian rhythm, autism spectrum disorder, neurodevelopment, genetics, synaptic plasticity, neurobiology, sleep

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social communication, limited patterns of interest and stereotypic and repetitive behaviors (American Psychiatric Association 2013). Research on the etiopathogenesis of ASD has gained pace with the formal statement on the increase in its prevalence of from 0.6% to 1.6% between 2000 and 2014 (Baio et al. 2014). Multiple different genetic, epigenetic, and environmental factors not yet clearly identified are believed to be effective on ASD (Anney et al. 2012, Hallmayer et al. 2011). Also, the roles of circadian rhythm disturbances and abnormalities in melatonin physiology in the etiopathogenesis of ASD have recently been subjects of interest and investigation. Variances in melatonin secretion are common in ASD, and given its neuroprotective and rhythm regulating effects, this hormone is thought to have a role in protection from neurodevelopmental disorders.

In this article, we aimed to look into the detail of research on the relationship between melatonin, circadian rhythm and ASD. For this purpose, the keywords, 'melatonin, circadian rhythm, autism spectrum disorder, neurodevelopment, genetics, synaptic plasticity, neurobiology, sleep' entered into the PubMed search engine covering the years 1990-2019 and the prominent research reported in the related literature were included in the review.

MELATONIN

Melatonin was discovered by the isolation of the molecule N-acetyl-5-methoxytryptamine from pineal gland tissue by Lerner et al. (1958), which was soon followed by the description of the pathway of melatonin synthesis in the pineal gland (Axelrod and Weissbach 1960). Although many organs other than the pineal gland have the capability of producing melatonin (Hardeland 2009); the diurnal rhythm of blood melatonin is exclusively the secretory function of the pineal

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gland (Naseem et al. 2014). The amphiphilic structure of melatonin, which is an indoleamine derivative with two functional groups, allows it to pass with ease through the blood-brain barrier and get dispersed in all body fluids. Hence, melatonin is also found in body fluids other than blood, such as the cerebrospinal fluid (CSF), bile, saliva, semen, ovarian follicular fluid, and amniotic fluid, and often at much higher concentrations than in blood (Carpentieri et al. 2012, Reiter et al. 2010). One of the earliest findings on the production of melatonin in the pineal gland is the display of a circadian rhythm in its synthesis and secretion determined by the prevailing light-dark cycle (Axelrod et al. 1965). Although the timing and the amount of melatonin secretion show large inter-individual differences, this is highly reproducible from day to day like a hormonal fingerprint in healthy individuals (Arendt and Skene 2005). Typically, melatonin levels increase to 60–200 pg/mL between 2 and 4 a.m. and decrease to 0–20 pg/mL during the day (Sae-Teaw et al. 2013). This fluctuation in melatonin levels throughout the day prepares the organism for nighttime/sleep or daytime/activity.

Melatonin is synthesized from tryptophan in the pineal gland by the sequential actions of tryptophan hydroxylase, decarboxylase, arylalkylamine N-acetyltransferase (AANAT), acetylserotonin O-methyltransferase (ASMT) or hydroxyindole O-methyltransferase (HIOMT) enzymes (Figure 1). Melatonin is metabolized firstly through hydroxylation by cytochrome p450 monooxygenases (mainly CYP1A2) in the liver, followed by conjugation with sulfate to form the metabolite 6-sulfatoxymelatonin (6-SM), which is excreted in the urine (Skene et al. 2001). The level of 6-SM is considered to reflect precisely the plasma levels of melatonin (Amaral and Cipolla- Neto 2018).

Synthesis of melatonin is started by the electrical signal sent from the suprachiasmatic nucleus (SCN) to the pineal gland and is regulated by the SCN according to the light/dark cycle over 24 hours. In mammals, the neural circuitry connecting the SCN with the pineal gland is remarkably complex. Whereas the neural circuitry is activated during the darkness; light inhibits neuronal activity and reduces the AANAT activity, resulting in suppression of melatonin synthesis (Kappers 1965, Moller 1979, Moore 1996, Maronde and Stehle 2007). The synthesized melatonin passes to the blood and the CSF through the third ventricle. Both blood and CSF melatonin can reach the SCN neurons and reset the circadian rhythm by influencing the firing rate of these neurons. Melatonin acts via mainly the G protein-coupled receptors (MT1 and MT2), orphan nuclear receptors (RZR / RORα), cytosolic receptors (MT3) on the cell membrane, or independently of cellular receptors (Jockers et al. 2016, Amaral and Cipolla- Neto 2018). The resetting and feedback effects of melatonin on the SCN are mediated mainly via MT1 and MT2 receptors in the SCN (Reiter 2010).

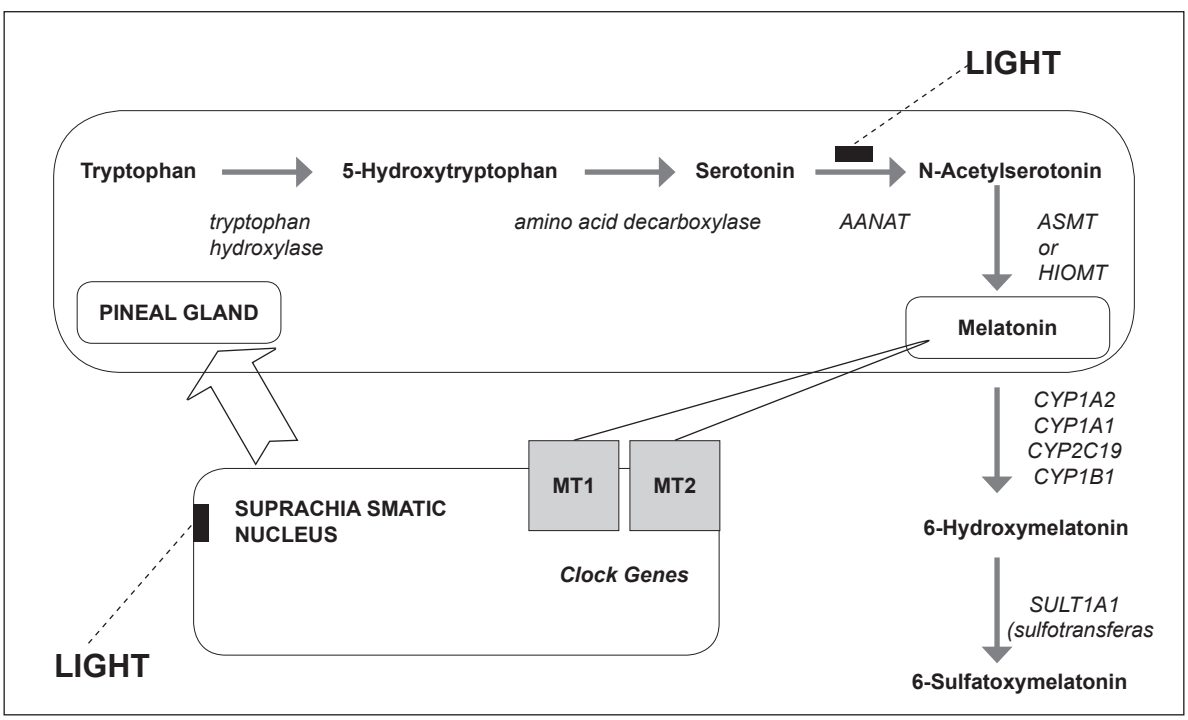

Figure 1. Melatonin Synthesis

AANAT: Arylalkylamine N-acetyltransferase; ASMT: Acetylserotonin O-methyltransferase (ASMT); HIOMT: hydroxyindole O-methyltransferase, MT1; MT2: G protein-coupled melatonin receptors; CYP1A2, CYP1A1, CYP2C19, CYP1B1: Cytochrome P450 monooxygenases

The Role of Melatonin in Neurodevelopment

The best-known function of melatonin is mediating the regulation of the circadian rhythm. However, melatonin is an important neurohormone with multiple physiological roles on sleep, thermoregulation, metabolism, anti-carcinogenic, anti-inflammatory, and antioxidative effects. Melatonin secretion doesn't start before approximately 9–15 weeks postpartum (Kennaway et al. 1996). The fetus is dependent on maternal melatonin since the pineal gland matures after birth. The maternal circadian melatonin rhythm is reflected in the fetal melatonin levels (Cohen et al. 2012). Maternal melatonin easily passes the blood-placental barrier and transmits photoperiodic information to the fetus ensuring the establishment of normal sleep patterns and circadian rhythms essential for normal neurodevelopment (Reiter et al. 2013). Maternal melatonin also passes easily into breast milk, and it is the source of the baby's melatonin during the newborn period. Melatonin, which is closely related to REM sleep, extends the duration of the REM state, whereas a lack of this hormone increases NREM periods (Tamura et al. 2008). Studies have shown that normal sleep patterns are essential for normal neurodevelopment occurs mainly during the REM state (Voiculescu et al. 2014, Tamura et al. 2008). In this context, it is believed that neurodevelopment of the fetus would be disrupted if REM sleep is impaired, and that melatonin is thought to regulate synaptogenesis and synaptic plasticity, thereby helping normal neurodevelopment (Morrissey et al. 2004, Kong et al. 2008, Merchant et al. 2013, Rossignol and Frye 2011, Tordjman et al. 2013). The fetal and neonatal neurodevelopment require a great deal of energy for cell differentiation and proliferation. In this period, which is highly susceptible to oxidative stress, the powerful antioxidant role of melatonin is also vital for neurodevelopment. It is thought that the level of adequate melatonin during pregnancy contributes to neuroprotection and the normal neurodevelopment of the fetus through the inhibition of excessive oxidative stress in the vulnerable central nervous system. Therefore, it is thought that the antioxidant effects of melatonin may reduce the risk of ASD. In a recent study, 6-SM levels in mothers of individuals diagnosed with ASD were found to be significantly lower than the control group (Braam et al. 2018). Given the fetal dependence on maternal melatonin supply through the placenta, melatonin deficiency in utero is proposed to be a risk or contributing factor to prenatal ASD (Pagan et al. 2014). If this proposal is validated by future studies, early intervention in individuals at risk would come into consideration.

The circadian rhythm of melatonin levels in the CSF synchronizes the biological rhythm with neuroendocrine functions. These fluctuations in melatonin levels are especially prominent in the brain ventricles, where the levels of melatonin can be almost 75-fold higher than in the plasma (Pang et al. 1990, Cardinali et al. 1997, Reiter and Tan 2002). One of the brain structures that may be especially sensitive to melatonin action is the hippocampus (Hogan et al. 2001, El-Sherif et al. 2002). A recent study has shown that melatonin increases dendrite formation, enlargement and complexity in the hilar and mossy neurons of the hippocampus in rats (Dominguez et al. 2015). Another study has shown that melatonin regulates neuronal plasticity in the hippocampus in mice by changing their excitability in response to repetitive stimulation (El-Sherif et al. 2003). In a valproic acid induced rat model of autism, impaired hippocampal serine/threonine kinase (CaMKII / PKC / PKA) phosphorylation was shown to recover by melatonin treatment. In the same study, it was also reported that melatonin treatment significantly improved social behavioral deficits (Tian et al. 2014).

Melatonin is also thought to play a role in neurodevelopment with its effect on excitation/inhibition (E/I) balance by causing changes in neurotransmitter levels (Wan et al. 1999, Zhang et al. 1999, Escames et al. 2001). A tight balance between excitation and inhibition in synaptic inputs in neural circuits is needed for normal brain development and function. Impairment of the E/I balance is therefore thought to play a role in the pathogenesis of neurodevelopmental disorders, including ASD. The hypothesis put forward by Rubenstein and Merzenich (2003), that an increased E/I ratio may be the underlying cause of sensory, social, and emotional differences in ASD, has since been supported by many clinical and neurobiological data (Gogolla et al. 2009, Nelson et al. 2015, Lee et al. 2017). Whether the E / I imbalance involved in the pathogenesis of ASD is due to increased glutamatergic signaling or decreased GABAergic signaling is one of the still unanswered questions. Regarding the hypothesis of Rubenstein and Merzenich (2003), melatonin is observed to have the ability to influence the day/night variations in glutamate and GABA levels, as well as modulating GABA induced currents (Wan et al. 1999, Wu et al. 1999, Marquez de Prado et al. 2000, Prada et al. 2005). On the other hand, serotonin also modulates GABAergic inhibition in the prefrontal cortex and temporal cortex (Yan et al. 2002). Consequently, it is possible that a defect in the melatonin synthesis pathway contributes to the pathophysiology of ASD by changing the balance between the glutamatergic and GABAergic synaptic currents through the effects on both melatonin and serotonin levels.

Melatonin Levels in Autism Spectrum Disorder

Chamberlain and Herman (1990) were the first to propose the hypothesis that there could be alterations in melatonin secretion in children with ASD. In the following years, several studies reported lower melatonin levels in individuals with ASD (Nir et al. 1995, Kulman et al. 2000, Tordjman et

Table 1. Studies on Melatonin Levels in Autism Spectrum Disorder

Study	ASD Study group	Control group	Measured variable	Findings
Ritvo et al. 1993	Young adults N:10 (18±2 y)	Healthy control N:10 (35±6 y)	Urinary melatonin level overnight collection and daytime sample	Significantly higher daytime melatonin level in the ASD group
Nir et al. 1995	Young men N:10 (23.9±5.1y)	N:5	Blood melatonin level every 4 h for 24 h	Significantly higher daytime melatonin level, lower nighttime melatonin level in the ASD group
Kulman et al. 2000	Children N:10	Healthy control N:20	Blood melatonin level every 4 h for 24 h	Decreased nighttime melatonin level in ASD No circadian variation in 10/14 (71.4%) children with ASD and inverted rhythm in 4/14 (28.6%) children with ASD
Tordjman et al. 2005	Children and adolescents N:49 (11.5±4.5 y)	Healthy control N:88 (11.0±4.4 y)	Urinary 6-SM excretion rate 12 h collection	Decreased nighttime 6-SM level in ASD 6-SM levels were negatively correlated with the severity of autistic impairments in verbal communication
Melke et al. 2008	Adolescents and young adults N:43 (F:14, M:29) (14.8±7 y)	Healthy control N:75 (F:30, M:45) (27±17 y)	Blood melatonin and serotonin level Platelet ASMT activity	Significantly higher serotonin level and low melatonin level and ASMT activity in the ASD group
Mulder et al.2010	Hyperserotonemic ASD group (elevated 5-HIAA, 5-HTlevel) N:10 (15.4±4.4 y)	Normoserotonemic ASD group N:10 (15.4±4.0 y)	Urinary6-SM excretion rate Platelet 5-HIAA, 5-HT level	Significantly lower 6-SM level in hyperserotonemic ASD group
Leu et al. 2010	N:24 (F:1, M:23) (5.7±1.9 y)	-	Urinary 6-SM excretion rate overnight collection	Significantly lower 6-SM level compared to laboratory control value, negative correlation between 6-SM levels and daytime sleepiness
Tordjman et al. 2012	Adolescents and young adults N:43 (F:12, M:32) (18.6±0.5 y)	Healthy control N:26 (F:7, M:19) (19.8±0.8 y)	Urinary 6-SM excretion rate daytime (12h) and nighttime (12h) for 24 h collection	Significantly lower daytime and nighttime 6-SM level in the ASD group, no circadian variation in 10/43 (23.2%) individuals with autism

ASD: Autism Spectrum Disorders, N: Number, F: Female, M: Male, h: Hour, y: Years, 5-HIAA: 5-hydroxyindoleaceticacid, 5-HT: 5- hydroxytryptamine, 6-SM: 6-sulfatoxymelatonin, ASMT: Acetylserotonin O-methyltransferase

al. 2005, Melke et al. 2008, Mulder et al. 2010, Tordjman et al. 2012), while two studies reported that daytime melatonin levels were significantly higher in ASD (Ritvo et al. 1993, Nir et al. 1995) (Table 1). The studies conducted up to now on melatonin levels in ASD in different cohorts using different methodologies indicate that an abnormal melatonin level is a consistent finding in ASD (Bourgeron 2007). The fluctuations of melatonin levels in blood and of urinary levels of the melatonin metabolite 6-sulphatoxymelatonin (6-SM) reflect the circadian rhythm of approximately 24 hours. In this respect, finding whether melatonin secretion does not show the circadian rhythm or its shows reversed circadian rhythm is significant (Kulman et al. 2000, Tordjman et al. 2012). Investigation of the relationship between melatonin levels and the severity of ASD showed that 6-SM levels were significantly lower in patients with ASD as compared to the controls and showed a negative correlation with verbal communication and ASD symptom severity (Tordjman et al. 2005). The same group later demonstrated that the nocturnal urinary level of 6-SM correlated negatively with verbal language development level, imitative social play and repetitive use of objects (Tordjman et al. 2012). These findings support that abnormalities in melatonin physiology may be linked to the pathophysiology or behavioral expression of ASD.

Studies investigating the causal mechanisms underlying the abnormal melatonin levels in ASD focus on the melatonin synthesis pathway and especially on AANAT and ASTM enzymes that act in the steps after serotonin (Figure 1). A relationship has been suggested between the 14-3-3 and miR-451 proteins which regulate AANAT and ASMT activities and the impairments in the steps of melatonin synthesis in ASD (Pagan et al. 2017). Melke et al. (2008) suggested that the lowered blood melatonin levels in ASD are associated with the lowered ASTM activity after demonstrating increased incidences of rs4446909 and rs5989681 single nucleotide polymorphisms on the ASTM gene. Demonstration of increased serotonin (Hallam et al. 2006), lowered melatonin (Abney et al. 2001) and ASTM activity in families including members diagnosed with ASD draws attention to the inheritance of altered melatonin synthesis. Biochemical anomalies such as significant elevation of the thrombocyte

level of platelet N-acetylserotonin (NAS), an intermediate of the melatonin synthesis pathway, was demonstrated in ASD patients and especially the mothers, as compared to the fathers of ASD patients (Pagan et al. 2014). N-acetylserotonin (NAS) is an inhibitor of tetrahydrobiopterin synthesis, a cofactor of several pathways such as nitric oxide formation and tyrosine/ bioamine synthesis. Therefore, in addition to the possible consequences of differences in serotonin and melatonin levels, NAS accumulation is also a factor that may play a role in the pathophysiology of ASD.

There are studies on melatonin receptors on a smaller scale than on melatonin biosynthesis. The G-protein (GPR50) coupled melatonin receptor genes MTR1A and MTR1B were shown to have variants to the extent of 2.8% in individuals with ASD diagnosis, as compared to 0% in healthy control individuals (Chaste et al. 2010). This observation was not confirmed by others (Jonsson et al. 2010). The mutations in the melatonin biosynthesis pathway enzymes AANAT and ASMT, the melatonin receptor genes MTR1A and MTR1B and the GPR50 protein have been demonstrated in too few ASD individuals to explain the generalized low levels of melatonin in ASD (Rossignol et al. 2011, Pagan et al. 2017).

CIRCADIAN RHYTHM

Circadian rhythm or 'circa-diem', meaning 'about a day' is a complex biological timing system that interacts with environmental factors and controls a different variety of physiological and behavioral processes. Light is the most important environmental stimulus (zeitgeber; time-giver) for entraining circadian rhythms. The stimulation by light incident on the retina is conveyed via the retinohypothalamic (RHT) tract to the suprachiasmatic nucleus (SCN) and the circadian rhythm of the body is synchronized to the 24-hour cycle in the natural environment (Dibner et al. 2010, Hasting et al. 2003). The SCN is accepted as the master clock of the brain, which synchronizes all functions by integrating the information from the periphery to form consistent systemic rhythms in the organism. Circadian rhythm controls a variety of biological processes in living systems, ranging from bacteria to humans, the most distinct effect being the maintenance of the daily sleep and wake cycle (Lowrey et al. 2004, Bell-Pedersen et al. 2005). The many physiological functions regulated by circadian rhythm include body temperature, feeding behavior, hormone secretion, xenobiotic metabolism, glucose homeostasis and cell-cycle progression (Takahashi et al. 2008). On the other hand, recent studies in the field of cognitive and developmental psychology have emphasized the importance of the motor, emotional, and relational rhythms and synchronicity in the early development of social communication (Tordjman et al. 2013). Under the conditions of impaired synchronization of the circadian clock network, functioning of motor, emotional and interpersonal rhythms alter causing susceptibility to psychiatric disorders such as ASD characterized by altered social communication (Charrier et al. 2016).

Circadian rhythm is regulated by clock-controlled genes (CCGs) found in many different tissues and cells. The genetic variations in CCG are thought to be capable of significantly affecting physiological functions and thereby potentially contribute to disease susceptibility (Takahashi et al. 2008). The important CCGs are listed as Per1, Per2, Per3, Clock, Npas2, Bmal1, Tim, Cry1, Cry2, Dbp and the Ck1e (Janich et al. 2011, Marcheva et al. 2010, Pachos et al. 2012). Behavioral effects of the anomalies in CCGs have been demonstrated to be related with sleep disorders in humans (Ebisawa et al. 2001, Toh et al. 2001), contextual memory in mice (Garcia et al. 2000) and communicative timing and memory formation in Drosophila (Sakai et al. 2004). The first hypothesis on the relationship between CCGs and ASD was put forward by Wimpory et al. (2002), with reference to both the concurrent and the developmental roles of social timing in social, communicative and symbolic deficits of ASD, and the suggestion that anomalies of the CCGs could have significant effects on development of ASD and especially on the communication disorders and timing deficits (Wimpory 2002). Investigation of SNPs in the 11-clock-controlled genes of 110 individuals with ASD and their families demonstrated significant allelic association with the Per1 and Npas2 genes (Nicholas et al. 2007). Another more recent study associated frequent mutations in ASD with the Per2, Per3, Clock, Bmal1, Tim, Cry1, Cry2, Dbp and Ck1ε genes (Yang et al. 2016).

The Role of Circadian Rhythm in Neurodevelopment

In recent years, the hypothesis most emphasized among those put forward by investigations of the effect of circadian rhythm on neurodevelopment was on the damaging effect of the anomalies of parvalbumin (PV) neurons on brain plasticity with likely contribution to neurodevelopmental disorders (Cabungcal et al. 2013). These inhibitory neurons distributed in the cerebral cortex synchronize the electrical activity of brain cells, playing a role in the timing of critical phases in brain development. Different hypotheses have been formed implicating the circadian rhythm having a direct effect as the cell-intrinsic timer of PV cells (Bartolini et al. 2013); that PV neurons can be affected by the oxidative damage, given that CCGs have been shown to regulate redox homeostasis in the brain (Musiek et al. 2013), and that the downregulation of the PV neuron maturation would result in impairment of the critical timing of plasticity phases (Hensch et al. 2005). Recently CCGs have been shown to control the critical onset phase of plasticity in the neocortex

of mice with CCG mutations. It was found that despite an intact master timer in the SCN, the PV cell-specific Clock or Bmal1 conditional knockout mice exhibited delayed critical phase timing, which was restored by pharmacological enhancement of GABAergic transmission; and the study implicated the role of the CCGs external to the SCN in neurodevelopment. Further, the Clock-Bmal1 activity, with its tight links to environmental factors such as stress, sleep deprivation, nutrition, can influence the critical plasticity phase (Kobayashi et al. 2015). These findings may be a well-known example of gene-environment interaction in psychiatric disorders. It was recently reported that PV knockout (PV-/-) or heterozygous (PV+/-) mice display behavioral phenotypes with relevance to all three core symptoms of ASD such as abnormal reciprocal social interactions, impairments in communication and repetitive and stereotyped patterns of behavior (Berger et al. 2012, Wöhr et al. 2015). Consequently, these findings support the hypothesis that PV cells may play a role in the etiopathogenesis of ASD.

Sleep Circadian Rhythm and Autism Spectrum Disorder

Sleep disorders are more common in children with ASD compared with typically developing children and those with intellectual disability. The prevalence of sleep problems in ASD is 50–80% compared to 9–50% in age-matched typically developing peers (Polimeni et al. 2005, Doo and Wing 2006, Allik et al. 2006, Giannotti et al. 2008, Richdale et al. 2009, Kotagal and Broomall 2012). Hypotheses regarding biological causes of sleep problems in children with ASD include neural organizational and maturational differences, CCG anomalies and abnormal melatonin secretion (Souders et al. 2017). Interviews with parents of children with ASD showed that more than 70% of patients had delayed development of the circadian sleep-wake cycle by at least 5 months (Segawa et al. 1982, 2006). The sleep disturbances in ASD may exacerbate core symptoms and related problems, including social interactions, repetitive behaviors, affective problems, and inattention/hyperactivity (Schreck et al. 2004, Gabriels et al. 2005, Malow et al. 2006, Goldman et al. 2009). Other behavioral parameters that have been associated with poor sleep in children with ASD include repetitive behavior, including compulsive behavior, and oppositional and aggressive behavior, anxiety, depression, and mood lability (Malow et al. 2006, Goldman et al. 2009, Mayes and Calhoun 2009). While, in the past, the abnormalities of sleep were considered as an epiphenomenon of ASD, today, in the light of recent neurobiological data, sleep disorders in ASD are becoming the target of requisite treatment.

MELATONIN TREATMENT IN AUTISM SPECTRUM DISORDERS

Demonstration of low melatonin levels in ASD has been suspected to be one of the causes of sleep disorder leading to investigation of the melatonin supplementation (Ritvo et al.1993, Nir et al. 1995, Kulman al. 2000, Tordjman et al. 2005, Melke et al. 2008, Mulder et al. 2010, Tordjman et al. 2012). Studies investigating melatonin supplementation in children with ASD have shown melatonin to be an effective, safe and well-tolerated treatment for sleep disorders and has been included in most treatment guidelines (NICE 2011). Fewness of the studies on melatonin treatment in adults limit the conclusion on effectiveness. The melatonin preparations used in ASD patients include the immediate-release type which facilitates falling asleep while the controlled-release type helps maintain sleep better (Rossignol et al. 2011). In Turkey only an immediate-release 3mg melatonin tablet is presently available. Most studies on melatonin supplementation in ASD have used the immediate release form, and some have relied on the combined immediate and controlled release form or the controlled release form. Additional placebo-controlled studies are needed to examine the differences in the effects and side effects of these preparations. The majority of children respond to a 1 or 3 mg dose given 30 min before bedtime with improvement in sleep latency (Rossignol et al. 2011, Tordjman et al. 2013, Bruni et al. 2015). In a recent meta-analysis on 18 ASD study groups given melatonin treatment, improvements were reported in sleep duration, sleep onset latency, and nighttime awakenings (Rossignol and Frye (2011). In addition to positive sleep-related effects, improvement have been reported in communication (Wright et al. 2011), social withdrawal (Gianotti et al. 2006, Malow et al. 2011), stereotyped behaviors (Malow et al. 2011, Garstang et al. 2006) and anxiety (Gianotti et al. 2006, Wasdell et al. 2008). In a randomized, placebo-controlled double-blind crossover study, Wright et al. reported that melatonin significantly improved sleep latency and total sleep compared to placebo, however it had no effect on the number of night awakenings. Though it was reported that there was a significant improvement in communication, the results were not detailed with regard to verbal or non-verbal communication (Wright et al. 2011). An open-ended study reported that melatonin treatment in children with ASD significantly reduced sleep latency, number of night awakenings and increased total sleep time, such that several families and classroom teachers commented that the children were easier to manage and less rigid in their behavior while taking melatonin (Garstang et al. 2006). In another randomized placebo-controlled study, melatonin combined with cognitive–behavioral therapy (CBT) proved superior to melatonin only, CBT only and placebo in reducing symptoms of insomnia in children with ASD, aged 4-10 (Cortesi et al.

2012). It should be kept in mind that some of the reviewed melatonin treatment studies here have major limitations, such as small sample size, heterogeneous subjects including both individuals with ASD and with other developmental disabilities and a wide age range (Garstang et al. 2006, Wasdell et al. 2008, Wright et al. 2011). This is a problem given that pineal melatonin secretion is influenced by age and pubertal stage. Therefore, more studies with larger samples in different age groups are needed to draw definite conclusions.

It is also reported that some individuals experienced a loss of response during melatonin treatment. The hypothesis claiming that this loss of response is associated with slow melatonin metabolism was first suggested by Braam et al. The hypothesis was investigated in 15 individuals, 7 of whom were diagnosed with ASD, and 4 had SNPs on the gene of the enzyme CYP1A2. The slowed down metabolism of this enzyme was found to extend the normal melatonin metabolism of 35-45 minutes up to 5 hours, leading to increased melatonin levels during daylight hours and the loss of the normal circadian rhythm of melatonin (Braam et al. 2010, 2013). The incidence of SNP in the CYP1A2 gene ranges within 12-14% in the general population (Butler et al. 1992, Nakajima et al. 1994) but this is thought to be much higher in neurodevelopmental disorders (Braam et al. 2013, Bruni et al. 2015). A retrospective investigation on 107 ASD diagnosed children under melatonin treatment reported 7 seven cases with initial sleep improvement which eventually worsened despite dose escalation. Improvement in sleep occurred in 3 children when the initial 3 mg melatonin dosage used in these 7 children was reduced to the 1.5–3 mg range (Andersen et al. 2008). Consequently, in cases of loss of response to melatonin treatment, the dose used may be reduced, rather than increased. Despite low incidence of adverse side effects of melatonin supplementation in children, the frequently observed side effects include morning drowsiness, increased enuresis, headache, dizziness, diarrhea, rash, and hypothermia (Gringas et al. 2012, Andersen et al. 2008, Wasdell et al. 2008). Slight transient headache and gastrointestinal symptoms are mainly reported during the first days of the treatment (Nagtegaal et al. 1996).

Melatonin is a pleiotropic neuroendocrine molecule with antioxidant, neuroprotective or immunomodulatory effects as well as hypnotic and chronobiotic effects. The widely comprehensive biochemical effects of melatonin could include the comorbidities of epilepsy, sleep and gastrointestinal problems next to the basic symptoms of ASD (Benabou et al. 2017). Melatonin synthesized in the enterochromaffin cells throughout the gut circadian variation in gastrointestinal melatonin is regulated by food intake and composition (Bubenik et al. 2002). Several animal studies have demonstrated that melatonin appears to influence the gastrointestinal system, such that low-dose melatonin increases intestinal motility, while a high dose of melatonin decreases intestinal transit in rats (Drago et al. 2002). Also, melatonin reduced the severity of intestinal inflammation in animal models of colitis (Carrillo-Vico et al. 2005, Zielinska 2016). It has been found that gastrointestinal dysfunction has a negative impact on sleep in children with ASD (Yang et al. 2018, McCue et al. 2017). It can be speculated that melatonin treatment can improve sleep, reduce pain and anxiety by ameliorating gastrointestinal symptoms in people with ASD. However, the effects of melatonin treatment on the gastrointestinal symptoms in ASD have not yet been clinically investigated (Gagnon et al. 2018). Furthermore, the difficulty of complaining of chronic pain or mild cold to caretakers by children with ASD (Moldofsky 2001, Chouchou et al. 2014), problems of sensory processing dysfunction and especially extreme sensory sensitivity, can contribute to sleep problems (Ben Sasson et al. 2007, Baranek et al. 2006). The promising results of animal studies on melatonin effects on pain have not yet been emulated in human studies (Gagnon et al. 2018). Further studies are needed to investigate the effect of melatonin treatment in children with ASD on comorbidities such as anxiety, depression, gastrointestinal dysfunctions, in addition to the treatment of sleep problems.

CONCLUSION

It is thought that melatonin might have a protective role in neurodevelopmental disorders with its hypnotic, chronobiotic, anti-inflammatory and antioxidant effects, and may direct neurodevelopment with its effects on early synaptic plasticity and neurotransmitter levels. Given the fetal dependence on maternal melatonin in the prenatal period, the question on the 'possibility of a protective role of early intervention on the reduced level of melatonin in ASD during pregnancy' comes to mind. The observed diversity in melatonin levels in healthy individuals currently precludes the determination of a reference value for the protective effect and the suggestion of an intervention. On the other hand, although alterations in melatonin levels are considered as consistent findings in ASD, the various hypotheses put forward to correlate this with pineal gland hypofunction, disorders of melatonin synthesis pathway and melatonin receptor mutation have not been backed up by the available data.

Next to the role of melatonin in regulating the circadian rhythm, melatonin levels also vary depending on the circadian system. Due to this bidirectional interaction, impairment in one of the systems can affect the other and create a greater impact. In addition to the recognition of the circadian system for its significant effects on human physiology, its effects on neurodevelopment is a current subject of interest and research. Despite the demonstration on animal models the effect of the CCGs on early synaptic plasticity, the emergence of ASD-like

symptoms with CCG mutations and the higher incidence of these CCG mutations in humans with ASD, the accumulated data is not still extensive enough to draw conclusions on the relationship of circadian rhythm and ASD.

Melatonin supplementation recommended as an effective and reliable agent to meet sleep problems in ASD with satisfactory outcomes and low side effect profile is another area of interest for clinicians. Sleep problems can also cause or exacerbate behavioral problems. In this context, sleep problems in ASD emerge as an important area of intervention. In clinical guidelines, melatonin treatment is recommended as the first pharmacological treatment approach after behavioral intervention for dealing with sleep disorders in children diagnosed with ASD. In spite of this, problems are still faced in clinical use of melatonin with appropriate dosage and formulation adjusted to the patient's needs, which is furthered in Turkey by the lack of health ministry approvals, limitations to the availability of preparations and high costs.

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