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Review

The relationship between autism spectrum disorder and melatonin during fetal development

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Abstract: Autism spectrum disorder (ASD) refers to the diverse range of neurodevelopmental disorders accompanying impairments in social interaction, difficulties in communication, and stereotyped or repetitive behaviors. Unlike the older term, autism, the newer term, ASD, better reflects the broad range of autistic symptoms and denotes a single diagnostic category of autism accompanied by numerous conditions. The pineal hormone melatonin is a well-known neuroprotectant and circadian entrainer. This hormone crosses the placenta and enters the fetal circulation, then conveys photoperiodic information to the fetus during pregnancy. These actions enable normal sleep patterns and circadian rhythms, followed by normal neurodevelopment. Melatonin also reduces oxidative stress, which is harmful to the central nervous system. Therefore, melatonin acts as a neuroprotectant and circadian entrainer, and may reduce the risk of neurodevelopmental disorders such as ASD.

Keywords: Autism spectrum disorder, Melatonin, Fetal development, neuroprotection, circadian rhythm

1. Introduction

Melatonin (N-acetyl-5-methoxytryptamine), a circadian rhythm-dependently synthesized and secreted hormone [1], was first structurally identified in 1958 [11, 12]. This hormone is produced mainly by the pineal gland, and other organs including the retina, Harderian gland, gut, bone marrow, platelets, glial cells, lymphocytes, pancreas, kidneys, and skin are also involved in the production of melatonin [2]. Melatonin is synthesized from its precursor, tryptophan, which becomes 5-hydroxytryptophan in a reaction catalyzed tryptophan hydroxylase [2]. Aromatic amino acid decarboxylase (AAD) converts 5-hydroxytryptophan into serotonin [2], which is then converted to N-acetylserotonin by arylalkylamine N-acetyltransferase (AANAT) [2]. This acetylated form of serotonin, N-acetylserotonin is converted to melatonin through the action of hydroxyindole O-methyltransferase (HIOMT) [2]. Melatonin is considered to have various biological functions, including the regulation of circadian rhythm [3] and sleep [4], anti-inflammatory functions [5], and antioxidant effects [6, 7]. Melatonin also plays a crucial role in fetal development. Because the pineal gland undergoes maturation after birth, the fetus is dependent on maternal melatonin. Melatonin can cross physiological barriers, including the blood-placenta barrier, without denaturation, and subsequently influences placental function [13]. During pregnancy, melatonin crosses the placenta and enters the fetal circulation, conveying photoperiodic information to the fetus. Consequently, melatonin affects the circadian rhythm of the offspring [14]. Therefore, a disrupted circadian rhythm

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may be attributed to abnormal melatonin concentrations. Improper melatonin secretion has been implicated in numerous neurodevelopmental abnormalities, including autism spectrum disorder (ASD) [15-17]. Because a normal sleep pattern is essential for neurodevelopment, a disrupted circadian rhythm due to abnormal melatonin concentrations may result in diminished brain growth and augment the risk of ASD [14, 19]. Furthermore, low parental melatonin levels may increase the risk of ASD in their offsring, indicating the importance of melatonin during fetal neurodevelopment [18]. We recently revealed a correlation between melatonin and ASD while suggesting prevention and therapeutic strategies for fragile X syndrome (FXS) with ASD. In this point of view, this review focuses on how melatonin affects fetal neurodevelopment and ASD.

2. Melatonin and its regulatory effects on circadian rhythm

2.1. Melatonin and its putative role in regulating fetal circadian rhythm

Circadian rhythm refers to the fluctuation in the internal environment in living creatures depending on a 24-h daily cycle [20]. Mammalian daily rhythms are mainly regulated by the circadian master clock, the suprachiasmatic nucleus (SCN), which is located in the anterior hypothalamus [21]. This master clock has numerous clock cells that synchronize the 24-h of biological clock [22]. In turn, peripheral oscillators in other brain areas and peripheral organs initiate secondary orchestration [23]. On a molecular level, key transcriptional activators circadian locomotor output cycles kaput (CLOCK), and brain muscle ARNT-like protein 1 (BMAL1), entrain circadian rhythms. Whereas intracellular CLOCK levels rarely fluctuate, BMAL1 increases in the morning, accompanying the binding of CLOCK and BMAL1 [24]. This heterodimerization of CLOCK and BMAL1 leads to the transcription of other clock genes including period circadian protein homologue (PER) and cryptochrome (CRY) during the day [25, 26]. At night, accumulated PER and CRY proteins form heterodimers, and translocate from the cytosol to the nucleus [26]. This complex then inhibits CLOCK-BMAL1 heterodimerization, and the resultant transcription of PER-CRY mediated by the CLOCK-BMAL1 complex is also terminated [25, 26]. The SCN regulates circadian secretion of the pineal hormone melatonin [27, 28]. As this pineal hormone crosses the placenta without any alteration, it freely enters the fetal circulation and conveys photoperiodic information to the fetus [14]. Melatonin receptors have been identified not only in the SCN but also in the peripheral organs of the fetus [14, 19]; thus, melatonin receptors are widespread in the fetus. Melatonin crosses the placenta and introduces the daily melatonin rhythm, which is characterized by high levels at night and low levels during the day, to the fetus [14]. Melatonin mediates organ functions according to the circadian cycle. Additionally, melatonin may play a crucial role in fetal neurodevelopment, because the normal sleep pattern, which is the circadian rhythm influenced by melatonin, is known to affect neurodevelopment [14, 19]. In this regard, melatonin may play a variety of roles, rather than being confined to circadian entraining (Figure 1.).

2.2. Regulatory role of melatonin in fetal development and neuroprotection

As described above, the normal sleep pattern is an important factor in neurodevelopment [14, 19]. The normal sleep pattern consists of two states: non-rapid eye movement (NREM), and rapid eye movement (REM) [29]. Studies have shown that neural development mainly occurs during the REM state [30]. In addition, human newborns sleep 16-18 h a day, and more than 50% of their sleep state is REM [31]. A newborn is likely to undergo vigorous neural development during REM sleep. In this context, the neurodevelopment of a fetus is disrupted if its REM sleep is disrupted [30]. REM sleep is closely associated with the pineal hormone melatonin. Melatonin extends the duration of the REM state, whereas a lack of this hormone increases NREM periods [19]. Furthermore, melatonin acts as a neuroprotectant in the fetus. Melatonin reduced the risk of cell death and inflammation in the fetal brain in an animal model of hypoxia [14, 32]. Clinically, melatonin can increased the survival rates of newborn babies with asphyxia by reducing oxidative stress [14, 33]. In summary, melatonin has been shown to affect REM sleep, and induce neuroprotection as well as neurodevelopment. Therefore,

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96 melatonin deficiency during development may be linked to neurodevelopmental disorders including
97 autism.
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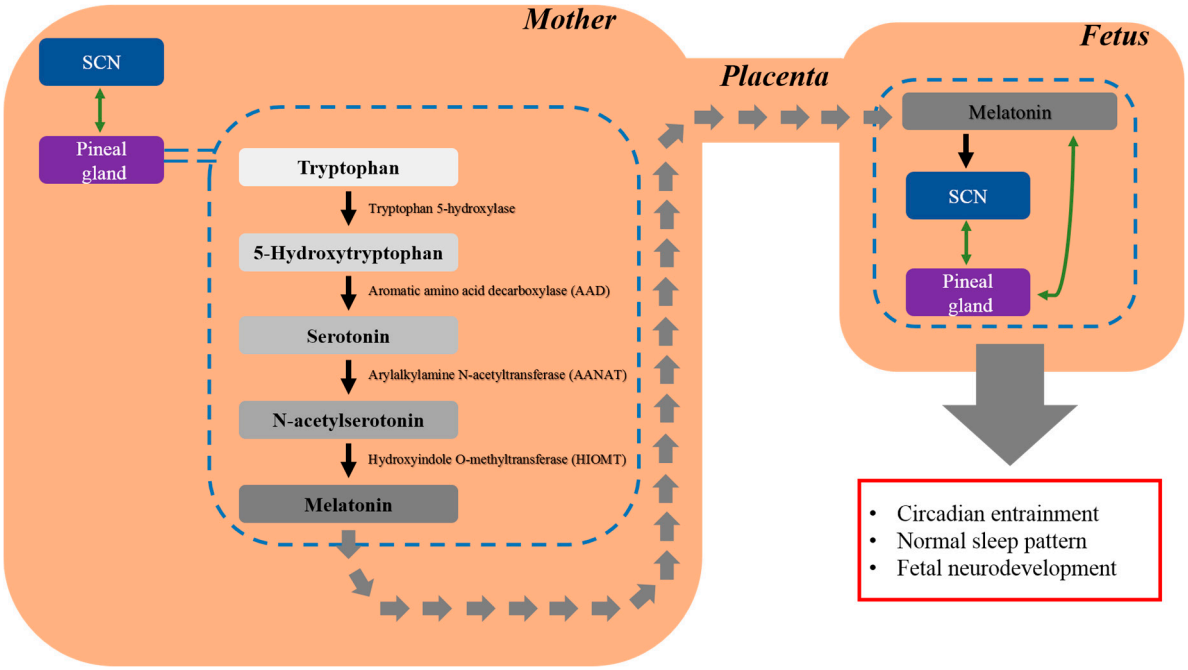

99

100 **Figure 1.** Maternal melatonin crosses the placental barrier to entrain the fetal circadian rhythm. Thus,
101 melatonin is present in the fetal brain prior to the maturation of the fetal pineal gland. After crossing
102 the placenta, melatonin entrains the fetal circadian rhythm, maintains the normal sleep pattern, and
103 protects the fetus from neurodevelopmental disorders such as ASD.

104

105 **3. Melatonin and its implications for autism spectrum disorder (ASD)**

106 *3.1. Overview of ASD*

107 Autism comprises a series of disorders that vary in severity, intellectual level, and functional
108 disability. The fifth revised version of the Diagnostic and Statistical Manual of Mental Disorders
109 (DSM-5) combined specific diagnoses and suggested the single broad ASD diagnosis [35]. ASD refers
110 to the range of neurodevelopmental disorders accompanying impairments in social interaction,
111 difficulties in communication, and stereotyped or repetitive behaviors. Because the symptoms of
112 autism vary enormously, the term "autism spectrum disorder" encompasses a single diagnostic
113 category of autism involving numerous conditions [34]. Whereas the older term, autism, described a
114 specific diagnostic category, the newer term, ASD, better explains this disorder by including multiple
115 conditions [34]. In this regard, the older term is being replaced by the newer term ASD. Genetic
116 disruption may give rise to synaptic deficits, and ultimately cause ASD. It has been revealed that
117 ASD-related genes are involved in common signal transduction pathways that are responsible for
118 synaptic development and neuronal plasticity [34].
119

120 *3.2. Abnormal melatonin secretion is implicated in ASD*

121 Melatonin was suggested as a potential therapeutic intervention for FXS with ASD in our
122 previous review article. In the article, FXS was the most common form of ASD and seemed to be
123 associated with the loss of fragile X mental retardation (fmr) gene products such as fragile X mental
124 retardation protein (FMRP), leading to diverse physiological and behavioral abnormalities.
125 Additionally, the mutation of this gene disrupts the normal sleep pattern and circadian rhythm.

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Subsequent alterations of melatonin synthesis and melatonin-dependent pathways may lead to autistic behaviors [34]. Melatonin is a well-known modulator of the regulation of neural plasticity and circadian rhythm [38, 39]. Thus, abnormal melatonin levels may destroy the circadian rhythm, and may even result in autistic behavior. Studies have reported decreased melatonin concentrations in individuals with ASD. Reduced levels of serum melatonin were found in autistic patients [15]. Other studies have demonstrated similar trends. According to Kulman et al., melatonin concentrations in autistic children are lower than those in normal children. They suggested that pineal hypofunction in autistic children may be the cause of these reduced melatonin levels [16]. Other researchers have also reported decreased nocturnal melatonin production in autistic individuals [36]. Also, as mentioned above, neurodevelopment mainly occurs during normal sleep. Therefore, children with neurodevelopmental disorders including ASD may suffer from pediatric insomnia. For these patients, melatonin may play a beneficial role not only as a neuroprotectant but also as a circadian entrainer [37]. In this context, abnormalities in melatonin concentration are likely to increase the risk of ASD.

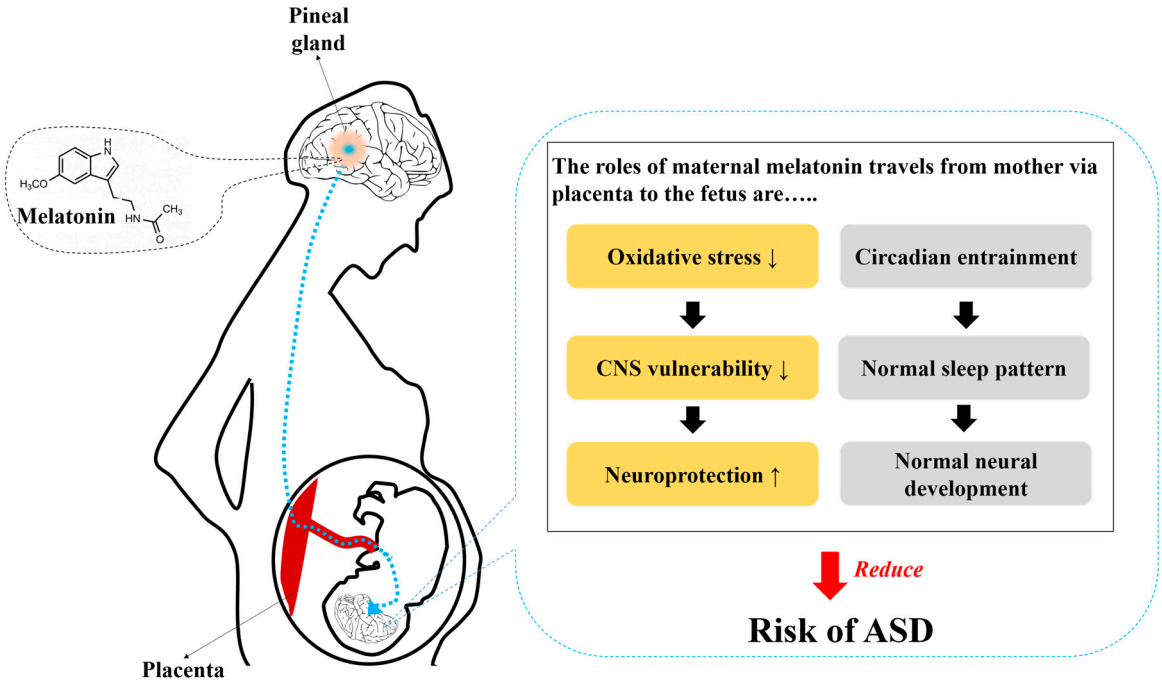

Figure 2. The beneficial roles of maternal melatonin that travels from mother via placenta to the fetus. The functions of melatonin in neuroprotection and circadian entraining may reduce the risk of ASD. Normal melatonin concentrations during pregnancy contribute to neuroprotection and the normal neurodevelopment of the fetus through the inhibition of excessive oxidative stress in the vulnerable central nervous system. Additionally, as adequate melatonin levels maintain the normal sleep pattern and circadian rhythm, normal melatonin secretion may also elicit neurodevelopment.

Melatonin is known to freely cross the placental barrier [40]. Even before the maturation of the pineal gland, which is responsible for melatonin secretion, melatonin can be detected in the fetal brain. Melatonin defends against neonatal inflammation and brain injury, evidenced by reduced post-inflammatory unfolded protein response (UPR) and normalization of autophagy following melatonin treatment [43]. Maternal and placental melatonin contribute to fetal neurodevelopment [41]. Thus, abnormalities in maternal melatonin levels may be linked to an augmented risk of fetal neurodevelopmental disorders [42]. Additionally, abnormal maternal melatonin may cause excessive oxidative stress [41]. As the central nervous system consumes a great deal of energy, has few endogenous antioxidants, including catalase and superoxide dismutase, and undergoes vigorous cell

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differentiation and proliferation, it is highly susceptible to oxidative stress [41, 44, 45]. Therefore, the antioxidant role of melatonin is vital for normal neurodevelopment, especially in the fetus.

Thus, mainly as a neuroprotectant, circadian entrainer, and antioxidant, melatonin is thought to protect the fetus from neurodevelopmental disorders and to relieve abnormal oxidative stress, and may reduce the risk of ASD (Figure 2).

4. Conclusion and perspectives

The properties of melatonin have been reported by a number of researchers. As described above, this hormone plays multiple roles, including neuroprotection and circadian entraining. Normal melatonin concentrations during pregnancy aid in neuroprotection and normal neurodevelopment of the fetus through the inhibition of excessive oxidative stress in the vulnerable central nervous system. Additionally, as the normal sleep pattern and circadian rhythm are maintained by sufficient melatonin levels, normal melatonin secretion may also influence neurodevelopment. Eventually, the well-known functions of melatonin in neuroprotection and circadian entraining may reduce the risk of ASD. Further studies are required to elucidate the potential risk factors.

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Conflicts of Interest: The authors declare no conflict of interest.

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