*Review*

# Melatonin as an Interventional Novel Candidate for the Individual with Autistic Fragile X Syndrome in Human

**Jinyoung Won** [1,2,3], **Yunho Jin** [1,2,3], **Tae Ho Lee** [4], **Sang-Rae Lee**[5], **Kyu-Tae Chang** [5*] and **Yonggeun Hong** [1,2,3*]

[1]  Department of Rehabilitation Science, Graduate School of Inje University, Gimhae 621-749, Korea; wy11167@naver.com (J.W.); jynh33@naver.com (Y.J.)

[2]  Ubiquitous Healthcare & Anti-aging Research Center (u-HARC), Inje University, Gimhae 621-749, Korea

[3]  Biohealth Products Research Center (BPRC), Inje University, Gimhae 621-749, Korea

[4]  Division of Gerontology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02115, USA; tlee3@bidmc.harvard.edu

[5]  National Primate Research Center (NPRC), Korea Research Institute of Bioscience and Biotechnology (KRIBB), Ochang 28116, Korea; srlee@kribb.re.kr

[*]  Correspondence: changkt@kribb.re.kr (K.-T.C); yonghong@inje.ac.kr (Y.H.);
Tel.: +82-43-240-6300 (K.-T.C); +82-55-320-3681 (Y.H.);
Fax: +82-43-240-6309 (K.-T.C); +82-55-329-1678 (Y.H.)

**Abstract:** Fragile X syndrome (FXS) is the most frequent monogenic form of autism spectrum disorder (ASD). Autistic FXS is caused by loss of the *fmr1* gene product, the fragile X mental retardation protein (FMRP), triggering physiological and behavioral abnormalities. It is correlated with clock components for behavioral circadian rhythm. Mutation of this gene causes the disturbances in sleep patterns and circadian behavior commonly observed in patients with autistic FXS, accompanied by frequent dysregulation of melatonin synthesis and melatonin-dependent signaling. These changes impair vigilance, learning and memory, and are also linked to autistic behavior including the abnormal anxiety response. However, although several possible causes, symptoms, and clinical features of ASD have been investigated, the correlation between an altered circadian rhythm and autistic FXS has not been extensively studied. Recent works have highlighted the impact of melatonin on the nervous, immune, and metabolic systems. Even though utilization of melatonin for sleep disorder in ASD has been considered in clinical research, further studies should be aimed at its neuroprotective role in ASD during developmental period. In this review, we focus on the regulatory circuits involved in melatonin dysregulation and circadian system disruption in those with autistic FXS. Additionally, we discuss the neuroprotective effect of melatonin intervention. This may improve neuroplasticity and physical capability. We also review the underlying molecular mechanisms, and suggest that melatonin may be a useful novel treatment for autistic FXS, countering the adverse effects of circadian variation.

**Keywords:** autism spectrum disorders; fragile X syndrome (FXS); sleep disorder; melatonin

## 1. Introduction

Autism spectrum disorder (ASD) and autism are commonly used to describe a group of neurodevelopmental disorders characterized by social deficits, communication difficulties, stereotyped or repetitive behaviors, and cognitive delay. In general, children with autism do not exhibit identical symptoms but, rather, vary extensively. As children with autism have several very different symptoms, the newer term ASD has been coined to describe a single diagnostic category of autism linking various conditions. Fragile X syndrome (FXS) is the most frequent form of inherited intellectual mental retardation, and is commonly considered to be a monogenic form of autism. The syndrome is characterized by clinical behavioral features including mental retardation, learning

disorder, attention-deficit disorder, hyperactivity disorder, anxiety, and epilepsy [1-3]. Notably, children with FXS often exhibit ASD characteristics or autistic behavior [4]. FXS is a genetic disorder caused by mutation of the fragile X mental retardation 1 (*fmr1*) gene on the X-chromosome. The mutation causes loss of the fragile X mental retardation protein (FMRP), in turn triggering physical and behavioral abnormalities. FXS individuals exhibit disturbed sleep and altered circadian behavior. In molecular studies, absence of the *fmr1* and *fmr2* gene alters the expression of clock gene-related components and changes the circadian rhythm. In addition, clinical studies have found that the sleep and behavioral alterations in FXS patients are associated with mutations in these two genes.

   Sleep disorder is general problem in children with ASD and also reported in up to 77% of children with FXS [5-7]. Furthermore, the occurrence of sleep disorder with FXS is associated with impaired vigilance, learning, and memory and also linked to autistic behavior with abnormal anxiety response [8-10]. Present studies reported that the children with ASD and FXS exhibited low level of melatonin and dysregulated circadian rhythm [11-15]. Melatonin is an endogenous neurohormone and synthesized predominantly in the pineal gland [16]. A major role of melatonin is to regulate the circadian rhythm that is related with biological functions of core body [17, 18]. A variety of neurobiological effect of melatonin are mediated through melatonin receptors and involved in neuronal plasticity [19, 20]. Otherwise, melatonin receptor independent pathway is unaffected by morphophysiological barriers including the blood brain barrier [21, 22]. In clinical, melatonin is commonly used for insomnia, and also applied in children with autism [23]. And experimental studies reported that melatonin treatment could attenuate sleep disorder without side effect [24]. In this paper, we discuss the effect of circadian dysregulation on physical and behavioral abnormalities. And we focus on the individual with autistic FXS that is the common monogenic type of autism and associated with circadian rhythm via *fmr* gene.

   Several studies reported that oxidative stress induced brain dysfunction and increased biomarker of oxidative injury was observed in ASD brain [25]. A number of lipofuscin containing neuron resulting from oxidative stress exhibited in language related cortex in ASD. These studies have indicated a decrease of cellular antioxidant and altered redox metabolism in ASD [26-28]. The functional consequence in terms of oxidative stress could induce superoxide production, oxidative protein and DNA damage. These results could contribute to the development of physiological abnormalities and psychiatric disorder in ASD. Markers of oxidative stress have linked to various neurological disease, ageing and also autistic FXS [29]. Individuals with autistic FXS have reported a higher level of oxidative stress. There is an increased response of reactive oxygen species (ROS) that is the cause of FMRP deficiency [30]. In the Fmr1 knockout (KO) mice model, a validated model for the FXS, the antioxidant system is deficient [31] and that lead to the pathophysiology of FXS. Oxidative stress signals involve the participation of reactive oxygen species (ROS) included roles of apoptosis and induce the brain damage [32,33]. These oxidant factors could lead to neurotoxicity and neurodegeneration [34-36]. The prevention of oxidative stress with melatonin based therapeutics has emerged as a new approach for treatment for the neurodevelopmental disorder such as autism [37,38]. A number of studies suggested that melatonin play roles as a very powerful free radical scavenger and antioxidant [39]. Indeed, recent studies reported the neuroprotective effect of melatonin in animal models of neurological diseases [40-42].

   Neuronal death following a severe brain injury, there is an acute dendritic and synaptic degeneration. Main characteristics of neuronal changes include cellular and synaptic alteration such as dendritic swelling and loss of synapses [43]. Dendritic spines of normal state neuron are bulbous heads shaped extensions at end of necks. However, an altered ratio of immature to mature spines has exhibited in damaged brain. In the Fmr1 KO mice that is FXS animal model, dendritic spines have exhibited abnormalities and immature morphologies that caused by FMRP deficiency. And overproduction of ROS due to the lack of FMRP has observed in Fmr1 KO mice. Eventually, these events affect neural signaling, learning and memory problem caused by altered antioxidant system [44]. Recently, melatonin has been investigated in neuronal plasticity with its antioxidant effect. In addition, other studies have reported the effect of melatonin on neuroplasticity and brain remodeling. Thus, we discuss the effect of melatonin on neural regeneration and physical capability in the

individuals of autistic FXS. Thus, we suggest that melatonin would be a novel treatment candidate for autistic FXS against adverse effect caused by circadian variation.

## 2. Autism spectrum disorder (ASD)

### *2.1. Classification of ASD*

Autism is the most frequent known as developmental disabilities in social interaction and communication. Many children with autism have commonly exhibited stereotyped behaviors with restricted and repetitive interests. Although, a number of study have been undertaken to elucidate the cause of autism, the exact cause of ASD has not been clearly defined yet. Since autism occurs with complex condition including genetic predisposition and environmental triggers, treatment strategy for autism has been unproven. Autism spectrum disorder (ASD) was proposed in the fifth revision of the American psychiatric association's diagnostic and statistical manual of mental disorders (DSM-5), that published in 2013. The child with autism not exhibits same symptom, but appears linked with various condition. Thus, the older term autism had described a specific category of diagnose, but newer term means a postulated spectrum disorder combined multiple conditions.

### *2.2. Causes of ASD*

#### 2.2.1. Genetic risk factors

Studies have consistently found that the cause of ASD is involved in hundreds of genetic variants. And ASD is strongly linked to genetic influence with high hereditary risk. In particular, gene associated with monogenic type of ASD participates in common signal-transduction pathways that are related with synaptic development and neuronal plasticity. The synaptic deficits in ASD has been induced by genetic disruption of protein synthesis or synaptic scaffold protein. There are monogenic forms of ASD by finding in FXS (loss of FMRP), Tuberous Sclerosis Complex (mutation of TSC1 or TSC2), Angelman syndrome (loss of Ube3a-dependent ubiquitination), and Phelan-McDermid syndrome (disruption of the Shank3 scaffold protein). These genetic disruption has been used for generation of ASD animal model for investigation and identification of promising targets for ASD treatment.

#### 2.2.2. Environmental condition: pre-, peri- and neonatal risk factors for ASD

Several prenatal, perinatal and neonatal complication have been indicated as potential risk factor for ASD. These risk factors include gestational diabetes mellitus, the first trimester vaginal bleeding, precipitation of medicine during pregnancy, viral and fungal infections, and meconium in the amniotic fluid. These factors have no conclusive relationship with ASD, but frequently exposed to ASD compared to normally developing children.  Environmental condition is divided into three categories: prenatal, perinatal and neonatal risk factors. During pregnancy, the following six factors were consistently related with ASD: advanced maternal and paternal age, primiparous woman, bleeding, medication, and diabetes. During the perinatal period, the following four factors were consistently related with ASD: induced labor, preterm birth, breech presentation and cesarean section. And a number of neonatal factors investigated as potential risk factors related with ASD: low birthweight and size, poor condition at birth including hypoxia, hyperbilirubinemia, encephalopathy and birth defects.

## 3. Fragile X syndrome (FXS)

### 3.1. Mechanism of FXS incidence

FXS is the most common genetic cause of autism [45]. Evaluations range that FXS affects approximately 1 in 3,600 male and 1 in 4,000 to 6,000 female [46]. FXS is occurred by mutation of fragile X mental retardation 1 (*fmr1*) gene at Xq27.3 on the X chromosome [47]. Mutation of *fmr1* gene is induced by methylation in the *frm1* promoter region and associated with the expansion of the CGG triplet sequence in the 5'-untranslated region (UTR). As a result, FMRP level is decreased or absent (Figure 1). Depending on the triplet repeat mutations in the *fmr1* gene, Fmr1 alleles are classified as normal, premutation and full mutation. In typical alleles, the *fmr1* gene contains 5-54 repeats of the CGG repeats, commonly 30 repeats. Premutation alleles have a number of CGG repeats, ranging between 55 and 200. Premutation of Fmr1 alleles is unstable and leads to expanding full mutation alleles, through maternal transmission [48,49].

### 3.2. Sleep problems in individuals with autistic FXS

ASD is neurodevelopmental disorders that indicate a common behavioral definition. In some studies, the severity of sleep problem was reported in children with autism and these children have a higher prevalence of sleep disorder than typically developing children [50-52]. And ASD with sleep problems have commonly showed the overactive and stereotypic behavior. Some studies suggest that abnormal regulation of melatonin may be related with sleep disorder in ASD. The sleep-wake cycle is related with circadian rhythm, and that is modulated by melatonin. The intrinsic cause of sleep disturbance is abnormal production of melatonin. And progressed sleep disorder is induced by dysregulation of melatonin synthesis, sensitization to environmental stimuli, and behavioral insomnia syndromes. Several sleep studies refer to correlation between sleep problem and melatonin's physiological role. However, relationship between blood level of melatonin concentration and pinealocyte synthesis of melatonin has yet to be established exactly. The exact causes of sleep problems in autism are not known.

### 3.3. Correlation between autistic FXS and circadian rhythms

Prevalence estimated of sleep problem in FXS with ASD is reaching higher as 80% than general population [53]. These sleep disruption leads to circadian variation and altered glucose homeostasis [54]. In experimental studies, mice lacking *fmr1* has exhibited abnormal circadian behavioral rhythm. Circadian variation including a loss of rhythmic activity in a light:dark (LD) cycle and a shorter free running period of locomotor activity in constant darkness (DD) is observed in Fm1 KO mice [55,56]. In addition, altered expression of clock component is also detected in FXS animal model. FMRP that overexpressed by using a transfection assay could increase Per1 or Per2 mediated BMAL1-NPAS2 transcriptional activity. These results suggest that FMRP is essential component for the regulation of rhythmic circadian behavior. Identically, the drosophila absent *fmr1* has shown the altered circadian rhythm. These results would indicated that fragile X related protein may be involved in circadian gene that lead to abnormal sleep pattern in FXS and play a critical role that regulating the circadian output pathway.

### 3.4. Neurodevelopmental abnormalities in autistic FXS

Almost Fmr1 KO mice exhibit neuronal abnormalities and immature morphology that revealed apparent features of dendritic spine. Dendritic spines existing on neuronal dendrite that is membranous protrusion have a bulbous head and a thin neck. Most spines provide synaptic strength and transfer electrical signals to axon terminal [57]. And dendritic spines express variable receptor related neurotransmitter and neurotrophic factor that serve as synaptic transmission. Among the abnormal dendritic spines, immature morphology is found in the Fmr1 KO mouse that has the lack of FMRP protein expression [58]. Fragile X syndrome patients exhibit abnormal dendritic spines structure that is associated with mental retardation [59]. In individuals with FXS, dendritic spine has

been reported commonly longer, thinner or fewer shorter than in normal individuals. These type of spine dysmorphogenesis is related with mental retardation [60,61]. In FXS mice, this abnormal spine morphology is exhibited that is characteristic of early development [62]. Structural and functional abnormalities of dendritic spine in FXS are induced by silencing of *fmr1* gene. The absence of FMRP results in dysmorphogenesis of dendritic spine and spine synapse number [63,64]. The specific role of FMRP synthesized near synapses is associated with synaptic structure and function [65]. FMRP is mRNA binding protein stimulating the synaptic protein synthesis that involved in neuronal synaptic plasticity. Thus, FXS that loss of FMRP in response to *fmr1* gene silencing is implicated in neurodevelopment abnormality.

## 4. Melatonin in autistic FXS

### 4.1. Melatonin signaling pathway under normal condition

Melatonin is a circadian synchronizer hormone that synthesized predominantly in the pineal gland during the night. A major role of melatonin is to regulate a biological signal of light and night cycles. A number of studies have reported the beneficial effects of melatonin. Melatonin has shown the antioxidative and neuroprotective effects, as well as involved in neuronal plasticity and network remodeling. Synthesis of melatonin begins during period of darkness through serotonin-NAS-melatonin pathway. Firstly, the amino acid tryptophan is uptaken into pineal gland. Serotonin based on the tryptophan is converted into N-acetyl serotonin (NAS) by N-acetylation with arylalkylamine N-acetyltransferase (AANAT). And then, NAS is converted into melatonin by acetylserotonin N-methyltransferase (ASMT) into melatonin [66].

### 4.2. Dysregulation of melatonin pathway in ASD

Dysregulation of melatonin synthesis has been observed in ASD compared with children with normal endogenous melatonin level. Significantly lower level of melatonin is proposed to contribute to the sleep disturbances in ASD. In addition, a significant decrease of gene encoding AANAT that is enzyme converting serotonin into NAS is observed. Since melatonin has been exhibited to have antianxiolytic effects, ASD that shown the impaired serotonin-NAS-melatonin pathway would be shown the circadian problem. Recent studies reported disruptions of the serotonin-NAS-melatonin pathway is highly sensitive and represent as a useful biomarker for ASD [67,68].

### 4.3. Correlation between melatonin and neurodevelopmental abnormalities in autistic FXS

In the case of FXS, deficits in neuronal plasticity are directly related to problem with the learning, memory, and cognition. Recent research have reported that FMRP modulates the synapse number, function and maturation. It is associated with protein synthesis dependent synaptic plasticity [66]. As FMRP is an influential regulator of dendritic protein synthesis, the synaptic changes with synaptic plasticity are observed in FXS [69]. In particular, FMRP is localized in the neuronal dendrite and synapse. FMRP is thought to play a role in the regulation of local protein synthesis such as mGluR through mRNA trafficking. Thus, FMRP regulates mGluR activity as a shuttle of mRNA [68, 69]. However, a lack of expression of FMRP induced neurodevelopmental disorder has affects long lasting enhancement in neuronal synapse.

An activation of mGluR occurs internalization of postsynaptic AMPA receptors that modulated by the rapid translation of protein for long term depression (LTD) [70]. A lasting patterned stimulus affects neuronal synaptic plasticity that achieved by long term potentiation (LTP) or LTD. These long lasting enhancements tend to improve learning and memory. LTP could change synaptic strength as a result of morphological change of postsynaptic neuron. And LTD could serves decrease of postsynaptic receptor density that is order to eliminate old memory for formation of new connection caused by LTP. These processes are necessary to maintain efficiency of synaptic network development. Thus, these mechanisms allow to receive the new information continuously, through elimination of insignificant and old memory.

However, mice model with fragile X syndrome produce excessive LTD protein. Actually, FMRP acts as an inhibitor of further translation of LTP protein. As the activation of mGluR triggers over-synthesis of LTD protein resulted from lack of FMRP, neuronal synapses in the shape of elongated and weak spine morphology have been expressed in hippocampus and cerebellum [71]. These results indicated that abnormal structure of neuronal synapse affects negative effect on the synaptic plasticity. Thus, inhibition of mGluR could contribute to suppress the mGluR-LTD signal instead of FMRP.

In experimental studies, excessive signaling of mGluR activation was reported in Fmr1 knockout mice [72]. The normal function of FMRP is believed to be a translational repressor and negatively regulates mGluR [73]. FMRP is an RNA binding protein that is involved in the transcriptional regulation and transport of specific mRNA [74]. And FMRP has reported that is highly observed in cytoplasm of neuron and localized in dendritic spines to regulate the translation of ribosome [75]. However, in a loss of function in FMRP, this balance is lost. Accordingly, the absence of FMRP accelerates excess of mGluR5 signaling that cases interfere with melatonin synthesis [76].

Melatonin is secreted by pinealocyte and glutamate receptors especially type 5 were expressed in the pinealocytes. Recent studies have implicated abnormalities in melatonin secretion and circadian pattern in individuals with autistic FXS. These results is caused by excessive signal transmission concerned with metabotropic glutamate receptors (mGluRs). These receptors are a type of G protein coupled receptors (GPCRs) and is classified into three groups. Receptor is divided group I, II, and III based on receptor structure and physiological activity [77]. The mGluR group I, including mGluRs type 1 and 5, is coupled to the G protein subtype, Gq protein that is activating phospholipase C [78]. The mGluR group II, including mGluRs type 2 and 3 and group III, including mGluRs 4, 6, 7, and 8. The mGluR group II and III are negatively linked with G protein subtype Gi and Go. These groups inhibit the enzyme adenylyl cyclase and suppress the formation of cAMP [79].

Norepinephrine (NE)-dependent melatonin synthesis that controls circadian rhythm and alleviates epilepsy is suppressed by released glutamate [80]. Also, metabotropic glutamate receptors group II, mGluR3, negatively regulates melatonin synthesis in the pinealocyte [81]. Some studies reported that metabotropic glutamate receptors type3 and type5 (mGluR3, mGluR5) are expressed in the pinealocyte and are involved in negative regulation of melatonin synthesis through the inhibition of cAMP cascade. And group II agonists have been found to suppress melatonin synthesis and prevent N-acetyltransferase activity in the rat pineal gland [82]. Thus, irregularities on melatonin production in FXS is linked with abnormal melatonin signaling is linked with absence of genetic condition such as *fmr1* that regulate FMRP and glutamate receptor.

## 5. Interventional therapeutic approach of melatonin to autistic FXS: Clinical assessment

### 5.1. Effect of melatonin treatment for sleep disorder in autistic FXS

Sleep disorder is common in patients with neurological diseases [83-85]. Melatonin modulating the sleep pattern and the circadian rhythms is associated with development of ASD [86,87]. Higher prevalence of sleep disorder has reported in individuals with ASD. Survey research indicated that a prevalence of sleep problem is up to 89% of children with ASD, and also 77% of children with autistic FXS [53]. Sleep problem has been commonly exhibited with melatonin secretion. Recent studies have shown that melatonin or melatonin metabolite concentration in children with ASD was significantly lower than in normal children [88,89].

Melatonin is endogenous neurohormone produced from the pinealocyte that is neuroendocrine cell. Furthermore, melatonin is wildly used in the clinic for insomnia in children with various benefits that is no side effect, inexpensive, and efficacious for sleep problem [90]. Melatonin supplement have been suggested that could regulate sleep wake-cycles and is used for alleviation of sleep problem in clinical research. The benefits of melatonin have been examined through various studies. One study investigated the efficacy of melatonin in a group of 107 children from 2 to 18 years of age with autism [91]. In this study, parents of 25% of treated children no longer reported sleep problem, and 60% of treated children reported improvement of sleep concern. In other studies, abnormal melatonin

concentrations have been reported to be lower in autistic children than typically developing children [92].

### 5.2. Effect of melatonin treatment for cognitive-learning disabilities in autistic FXS

Sleep disorder progressed chronic state mainly affects additional learning and behavior problems in ASD. The functional consequences of abnormal melatonin in FXS may induce learning and memory problem. In Fmr1 KO mice, memory impairment have induced due to deficits in synaptic plasticity that is accompanied with immature dendritic spine. A number of studies have reported evidence that melatonin facilitates synaptic plasticity to enhance learning and memory mechanism. These studies have supported a correlation between loss of neuroplasticity and malfunction or irregularities on melatonin production in FXS.

Low levels of melatonin have been associated with GABAergic system [7]. Gamma-Amino Butyric acid (GABA) is the main inhibitory neurotransmitter of the CNS. GABAergic system triggers relaxing the brain and inducing sleep. Melatonin in the brain interacts with the GABAergic system, and stimulates GABAergic activity. Thus, abnormal melatonin levels affect influence the onset and length of sleep [93]. And altered circadian clock mechanism caused by abnormal melatonin synthesis could have an effect on sleep-wake cycle. Recently, studies using autism animal models suggest that clock and clock related gene may interplay with ASD. And the research using Fmt1 KO mice investigates the interactions of clock protein and sleep changes in FXS. There is also evidence that melatonin is helpful in treating sleep problems in autism with oxidative stress, and physical alteration of axon and dendritic spine [94,95].

### 5.3. Neuroprotective effect of melatonin on seizures in autistic FXS

Individuals with FXS are at a higher risk of neurological disease. Seizure is important characteristic of autism and FXS is significantly associated with seizures. Clinical survey data showed that epilepsy occurs in 10 to 20% of children with FXS [96]. According to a recent study, melatonin has been reported that could be effective for regulating sever epilepsy [97]. Melatonin, which is used for treating sleep disorder without side effect, has suppressed the incidence of epilepsy.

Epilepsy caused by brain injuries and chemical imbalances is a neurological disease resulting from biochemical responses. Particularly, free radical is linked to seizure initiation [98]. Excessive production of free radicals contributes to brain damage in neuropathy patient including stroke, neurodegenerative disease such as Alzheimer's disease and Parkinson's disease [99]. Oxidative stress is occurred in mitochondria arising from seizure. Seizure is one of the primary causes of oxidative stress that induced neuronal cell death. Recently, melatonin is discussed in relation to epileptic seizure [100-102]. Melatonin has been known for antioxidant as a free radical scavenger. Furthermore, a large study indicates that melatonin may play a role of promising anticonvulsant resulting in its antiepileptic activity. In clinical study, low melatonin base line was exhibited in patients who suffered from epilepsy, and increased dramatically after a seizure. These results suggest that melatonin may play a role in regulating and preventing seizures. However, other studies reported that melatonin have possibility the risk of seizure and may increase the seizure incidence. These arguments provide evidence that melatonin affects hippocampal excitability and increases the susceptibility of seizure by lowering the threshold [103]. Thus, the role of melatonin in epilepsy remains under debate.

### 5.4. Synergistic effect of melatonin on synaptic plasticity in autistic FXS

Recently, melatonin has been reported that could act as neuroprotective agent against neurological injury [104-107]. In experimental study, rodents injected with melatonin plus dexamethasone that has a neurotoxic action on hippocampus has been demonstrated the neuroprotective effect of melatonin. Abnormal hippocampal cells are reduced and histological difference are found compare with vehicle group. Melatonin is endogenous neurohormone which regulates several biological functions. And also, exogenous melatonin has shown the preventing effect on neuronal cell death and cognitive dysfunction [108].

In addition, neuroprotective effect of melatonin could be confirmed in acute global cerebral ischemia and hypoxic ischemia [109]. Most of cerebral ischemic model has been found a significant loss of neuron in hippocampal region range of CA1 to CA4. In case of children with perianal hypoxic ischemia, brain injury is directly caused by neuronal cell death, and remains chronic neuropathic diathesis, such as cerebral palsy, mental retardation and epilepsy [110]. Brain damage due to cerebral ischemia is primarily induced by reduction of blood supply including oxygen supplement.

As blocking of blood supply, cellular metabolic system is converted into anaerobic metabolism. Consequently, negative factors such as depletion of ATP, accumulation of lactic acid and cellular input of calcium are occurred. However, melatonin treatment group has been shown that melatonin could protect against brain damage and delayed neuronal cell death. Under reperfusion condition after cerebral artery occlusion, over produced free radical lead to trigger activation of oxidative stress. Melatonin has able to suppress brain damage from oxidative stress. As the neuroplasticity is recognized in learning, memory and recovery of brain damage, melatonin also must be expected to conduct research into relationship between melatonin and autism. Interestingly, delayed stabilization and abnormal morphological features in dendritic spine is main characteristics of FXS. These distinct features are related with impaired synaptic signaling and connection. The disruption of excitatory synapse pruning and hyper connectivity is primarily found in FXS patients and the Fmr1 KO mouse due to loss of post synaptic FMRP [111]. A deficit of FMRP resulting in this incomplete pruning induces cell to cell hyper connections in synapses. The connection pruning process that observed during early development is essential to formation of neuronal circuit. However, FMRP loss of function causes hyper connectivity and excess synapses in FXS leading to autistic features. Melatonin is also associated with neurogenesis linked with microtubule polymerization on dendrite. Thus, melatonin could stimulate dendrite maturation and affect neuroregeneration.
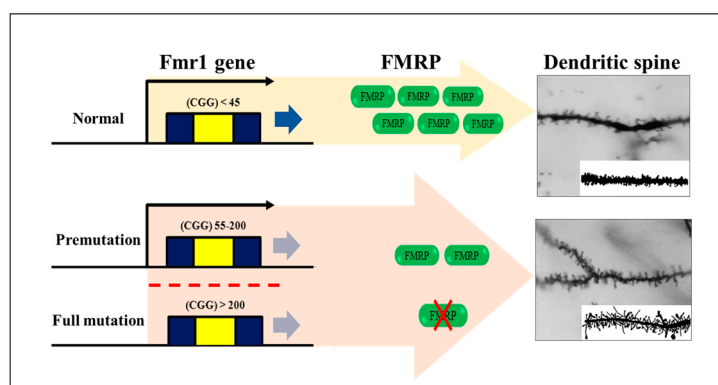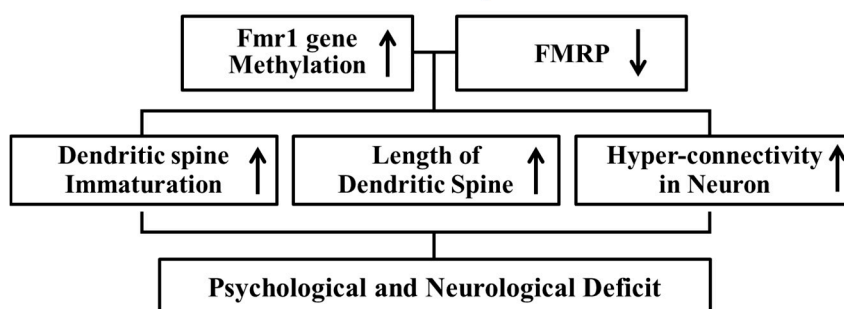


**Figure 1.** Diagram of transcription and translation of the Fmr1 gene [47-49]. FXS resulted from the expansion of a CGG trinucleotide repeat in the 5' untranslated region of the fragile X mental retardation 1 (*fmr1*) gene. Dendritic spine morphology between Fmr1 KO and wild type mouse [112]. Overabundance of immature dendritic spine (bulbous head and a thin neck) is expressed in Fmr1 KO mouse [63,65].

## 6. Conclusions

The field of autism is linked with extensive research into molecular biology and has infinite potentials of targeted treatment. We highlight a variety of neurological effects of melatonin in autistic FXS. In this review, we research the characterization of autistic FXS, monogenic form of autism, and investigate the prevention and therapeutic approach to FXS. The clinical application of melatonin based therapeutics that would lead to effective treatment and could be clearly beneficial in the prevention of disease. However, additional studies are needed to examine the mechanism of melatonin associated with autism and FXS. Further research is required to investigate the mechanism of interaction between melatonin and newly generated brain cells by increase of neurotrophic factors.

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