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MINIREVIEWS

Dysregulated cortical synaptic plasticity under methyl-CpG binding protein 2 deficiency and its implication in motor impairments

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Abstract

Caused by the mutation of methyl-CpG binding protein 2 (MeCP2), Rett syndrome leads to a battery of severe neural dysfunctions including the regression of motor coordination and motor learning. Current understanding has revealed the motor cortex as the critical region mediating voluntary movement. In this review article, we will summarize major findings from human patients and animal models regarding the cortical synaptic plasticity under the regulation of MeCP2. We will also discuss how mutation of MeCP2 leads to the disruption of cortical circuitry homeostasis to cause motor deficits. Lastly, potential values of physical exercise and neuromodulation approaches to recover neural plasticity and motor function will be evaluated. All of this evidence may help to accelerate timely diagnosis and effective interventions for Rett syndrome patients.

Key Words: Rett syndrome; Motor function; Motor cortex; Synaptic plasticity; Physical exercise; Methyl-CpG binding protein 2

Core Tip: In this mini-review, Zhang WJ summarized current findings for the synaptic plasticity in the cortex and related motor learning functions under the scenario of Rett syndrome. The discussion of neuropathological mechanisms can help us to better understand the disease progression and more importantly to develop more effective measures to counteract motor deficits.

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INTRODUCTION

Rett syndrome is one neurodevelopmental disorder that is caused by the genetic mutation of methyl-CpG binding protein 2 (MeCP2)[1]. Predominantly found in females with about a 0.01% incidence[2], Rett syndrome has been recognized as one of the major genetic conditions that affects neurodevelopment. As clinical features, about 61% of Rett syndrome patients developed autism spectrum disorder (ASD)-like symptoms[3], making it one major genetic contribution to autistic syndromes. Other behavioral features of Rett syndrome include cognitive and verbal disabilities[4] as well as the retardation of general development[5]. Among various clinical manifestations, deficits of motor function can be found in early stages of disease progression (around 12-18 mo in patients), as displayed by the gradual deterioration of normal motor functions and the occurrence of repetitive movements[6]. As a result, the gradual loss of acquired motor skill has been recognized as one prominent feature of Rett syndrome[7], further highlighting the relationship between motor functions and MeCP2. In this mini-review, we will summarize current major findings regarding motor dysfunctions in Rett syndrome and discuss their correlation with MeCP2-mediated synaptic plasticity of motor circuits, especially those in the motor cortex. In addition, we will also explore the possibility of non-drug intervention strategies including noninvasive neuromodulation and physical exercise in relieving these motor syndromes.

DYSREGULATED CORTICAL SYNAPTIC PLASTICITY IN RETT SYNDROME

Recent studies have demonstrated the pleiotropic functions of MeCP2 in mediating early events of neurodevelopment including neurogenesis, migration and patterning[8-10]. Deficits of neural network formation frequently lead to abnormal functions. In the cortical region, MeCP2 mutation disrupts the normal excitatory-inhibitory (E/I) balance, resulting in altered synaptic computation[4,7,11-13]. In specific studies, MeCP2-null knockout mice presented elevated GABAA and N-methyl-D-aspartic acid (NMDA) receptors in the barrel cortex[13]. However, using MeCP2-mutant mice, both excitatory and inhibitory conductance were reduced *in vivo* while the E/I ratio was increased[11]. In another study using MeCP2-mutant mice, cortical pyramidal neurons (PNs) displayed decreased spontaneous activity probably due to the reduced miniature excitatory postsynaptic currents (mEPSCs) amplitude while the inhibitory input did not change[12]. Those seemingly contradictory results further suggested the complicated mechanism of MeCP2 in mediating cortical network. A possible approach for further investigation can be achieved *via* cell type-specific study of MeCP2 function. For example, parvalbumin (PV)-specific MeCP2 deletion recapitulated reduced cortical excitability by global MeCP2 deletion[11]. Multiple mechanisms including ion permeability, neurotransmitter receptor or synaptic structural proteins can be further interrogated, as MeCP2 works as a transcriptional regulatory factor to potentially affect their gene expression. Since the neural plasticity of the cortical network is closely correlated with motor learning[14,15], the dysregulated function of MeCP2 may confer motor deficits. Further interrogation of MeCP2-dependent synaptic regulation can help to reveal the pathological process of related motor impairments in order to provide diagnostic and treatment targets.

When examining the neural mechanism of Rett syndrome-associated behavioral symptoms, it is suggested that MeCP2 works as one methyl-DNA binding protein[16]. The loss-of-function mutation of MeCP2 in Rett syndrome thus can be generalized as the deprivation of transcription repression, although recent studies are suggesting its multifaceted roles including activation or suppression of specific genes[17]. Across different brain regions, MeCP2 mediates the gene expressional network in a similar pattern[18], suggesting the brain-wide effect. When examining the transcriptional regulatory mechanism, a recent study identified the prominent role of MeCP2 in suppressing the initiation of gene regions with high CG-methylation levels[19]. For those non-CG methylated gene regions, MeCP2 also exerts a suppressor role *via* repressing enhancer activity[20]. In the exploration of MeCP2-targeted molecules, key modulators of neural plasticity have been recovered. For example, MeCP2 affects the transcription of BDNF to affect myelination and remyelination[21]. An early study further showed that MeCP2 associated with the transcriptional activator CREB1 to mediate a wide range of brain genes[17]. Moreover, MeCP2 interacts with a lot of neuronal genes in positive or negative manners. The transcriptional factor forkhead box protein O3 (FOXO3) has been found to be positively regulated by MeCP2 *via* deacetylation[22]. Those effects on transcriptional factors highlight the role of MeCP in the top layer of the gene regulatory network. Besides those transcriptional factors and neurotrophic molecules, MeCP2 also affects the post-translational modification of neuronal genes. For example, the histone modification

has been shown to be mediated by MeCP2 *via* recognizing H3K27me3[23]. Furthermore, the phosphorylation of MeCP2 itself adds further layers onto its regulatory network. The brain-specific phosphorylation of MeCP2 is known to regulate BDNF expression, contributing to neuronal growth and maturation[24]. In a broad sense, activity-dependent MeCP2 phosphorylation affects its interaction with transcriptional repressors[25], providing an epigenetic mechanism. During neurodevelopment, cell cycle-associated MeCP2 phosphorylation modulates adult neurogenesis[26] and nervous system functions[27]. Combining all these results, MeCP2 regulates the expression of neuronal genes *via* different pathways at transcriptional and post-transcriptional levels (Figure 1).

In neural tissues, gene transcription plays a critical role in various forms of synaptic plasticity such as the long-term potentiation (LTP) and long-term depression (LTD)[28]. People are thus beginning to dissect the neuropathological mechanism of Rett syndrome from the synaptic perspective[29]. Current knowledge has observed the disruption of normal synaptic plasticity under MeCP2 loss-of-function mutation across different brain regions including the hippocampus[30], the cerebellum[31], the visual pathway[32] and the amygdala nuclei[33]. As the critical region for high-order cognitive and mental regulation, the cortical region is also affected by MeCP2 mutations. For example, MeCP2 insufficiency in mouse auditory cortex affected the local network and disrupted maternal pup-retrieval behaviors[34]. In mouse primary visual cortex (V1), MeCP2 deficiency remarkably disrupted the early-stage development of neural plasticity during the so-called "critical period"[35,36]. The abnormal synaptic development resulted in the morphological deficits of synapse, including decreased spine density[37], altered spine morphology or dendritic complexity[38], shorter dendritic lengths[39] and alternation of synaptic protein expression in primary motor cortex (M1)[40,41]. Furthermore, the reduced neuronal size can be observed in layer V PNs of M1 in Rett syndrome model mice[42]. These findings provide the first-hand evidence for the disruption of structural and functional plasticity in the cortical region upon MeCP2 deprivation, highlighting the necessity and importance to elaborate the cortical neuropathology of Rett syndrome.

It is important to notice that both cell autonomous and non-autonomous mechanisms reside in MeCP2-mediated cell plasticity. For example, the loss of MeCP2 affects the autocrine brain derived neurotrophic factor (BDNF) signaling in excitatory neurons to affect neural plasticity, as wildtype neurons cannot rescue mutant cells in the area[43]. Such results provide further clues for clinical manifestations as mosaic patterns of mutations frequently occurs in Rett syndrome patients[44]. Although the primary cause of Rett syndrome is believed to be cell autonomous, non-autonomous mechanism has been revealed as the culture medium from MeCP2-mutated astrocytes disrupted dendritic morphology of wildtype hippocampal neurons[45]. Therefore, MeCP2 affects neural function *via* a complex network and further elaborations are required to study the cell-specific effect.

To attribute the factors for disrupted cortical synaptic plasticity under MeCP2 mutation, recent advances are highlighting the role of local inhibitory transmissions. In the mouse auditory cortex, independent lines of evidence are suggesting that the abolishment or insufficiency of MeCP2 suppresses normal activity of PV-interneurons, resulting in failures of maternal caring behaviors[34,46]. In primary somatosensory cortex (S1) and M1, the learning-associated modulation of plasticity of PV-interneurons was impaired in MeCP2 knockout mice as well as under heterogenous mutation of MeCP2[47]. In the barrel region, the loss of MeCP2 also enhanced glutamatergic transmission[13]. Such interruption of normal cortical network homeostasis might be explained by MeCP2 influence on synaptic plasticity during the critical period in early-stage development[36]. Such opinions were further supported by the conditional knockout of MeCP2 in PV-interneurons resulting in the absence of neural plasticity of V1 during the critical time[35]. To figure out the molecular mechanism, current studies are suggesting the role of neurotrophic factors. For example, BDNF was downregulated under MeCP2 deficiency[48]. As an intervention trial, insulin-like growth factor-1 (IGF-1) partially relieved such neurodevelopmental deficits under MeCP2 deficiency[49] and recovered cortical plasticity[50]. An alternative explanation exists in the cortical perineuronal nets (PNNs) whose formation is dependent on MeCP2[51]. Since PNNs are known to mainly surround PV-interneurons[52], the extracellular modulation may provide a model to explain how pan-neuronal mutation of MeCP2 leads to PV-interneuron specific defects.

The converging evidence of deficient GABAergic transmission upon MeCP2 mutation implies the hyper-excitation of the cortical network. In Rett syndrome patients, clinical recording supported such hypothesis by displaying significant increases of the excitation index of M1 in association with reduced short-interval inhibition[53] plus decreased inhibitory motor control[54]. Mouse model studies also suggested aberrantly high cortical excitability upon MeCP2 deficiency[49], probably due to diminished extracellular GABA transporter activity[55] or under-development of dendritic spines[40]. However, other studies supported the enhanced GABA transmission under MeCP2 knockout[13]. In a short summary, both presynaptic function such as GABA transporter and postsynaptic mechanism including spine formation and synaptic transmission are involved in MeCP2-mediated cortical plasticity. To better dissect the molecular pathway, cell-specific genetic manipulation and functional studies can be performed. For example, PV-specific MeCP2 deletion mimics the effect of global gene knockout[11]. In the future, MeCP2 can be studied in other neuronal and glial cell subpopulations in the cortex.

Based on these facts of disrupted cortical E/I balance, the application of neuromodulator drugs or neuromodulation stimulus may provide a promising future for region-specific intervention of motor symptoms under MeCP2 deficiency. In the last part of this article, we will summarize major findings

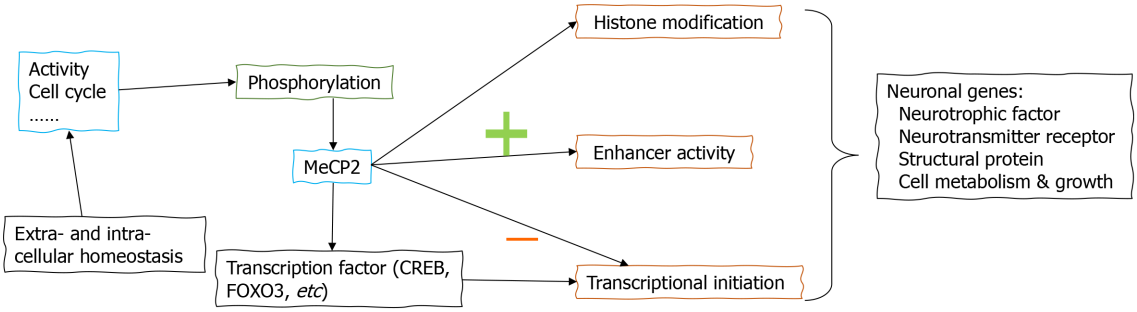

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Figure 1 Graphic illustration for methyl-CpG binding protein 2-mediated pathway of neuronal gene transcription. The activity of methyl-CpG binding protein 2 (MeCP2) is mediated by phosphorylation, which can response to cell cycle or cellular activity. MeCP2 exerts pluripotent functions at genetic and epigenetic layers, including directly or indirectly affecting gene transcription, or modifying chromatin structures. Such modulatory network eventually affects both structure and function of neurons[17-20,23,26].

and prospective regarding the neuromodulation approaches for alleviating motor symptoms of Rett syndrome.

SYNAPTIC DYSFUNCTION IN MOTOR CORTEX IN RETT SYNDROME AND RELATED MOTOR DYSFUNCTIONS

Among the major clinical features of Rett syndrome, motor deficits occur early during the disease development and persist across the whole disease process: The motor delay becomes apparent among 1.5-years-old and 3-years-old, after a seemingly normal early postnatal period[4]. During the adolescent and adulthood period, the progressively declined motor function can be presented as Parkinsonism-like features[56]. Such progression of motor symptoms usually develops into severe ataxia and deprives the patients of the ability to walk or stand during the teenage period[7]. These clinical manifestations can be replicated in mouse models: In MeCP2-null knockout mice, early-onset motor abnormalities were found to induce higher lethal rates[57]. In addition, these model animals presented regression of acquired psychomotor skills under a social interaction scenario[58]. These behavioral deficits clearly suggested the involvement of the motor system in Rett syndrome pathology.

Distinct brain regions and neural ensembles regulate voluntary movement, including the forebrain sensorimotor region, the midbrain nuclei such as the thalamus and basal ganglia, as well as the hindbrain regions plus the cerebellum. The motor cortex is innervated by distinct neuromodulator systems including dopamine, noradrenaline and serotonin. The brain-wide deficiency of MeCP2 thus may affect motor cortical plasticity *via* disruption of subcortical inputs. For example, the ablation of MeCP2 in aminergic neurons produced cell autonomous effects resulting in behavioral abnormalities [59]. The pharmaceutical potentiation of the serotonergic pathway improved cortical microcircuits and recovered motor learning behaviors[60]. Another study further revealed that striatal MeCP2 was critical for maintaining dopaminergic transmission of psychomotor regulation[61]. These findings supported the indispensable role of MeCP2 in the neural network related with cortical activity.

Although the site-specific gene knockout study has suggested the role of MeCP2 in mediating motor behaviors across different neural networks such as the noradrenergic transmission, the motor cortex remains as the prominent brain region in which fine motor control is regulated. Within the motor cortex, both excitatory PNs and GABAergic interneurons form the local network to drive the voluntary movement. PNs were once believed to be the principal projecting neurons in the cortical region and their structural and functional plasticity largely affects motor functions[62,63]. MeCP2 was known to mediate synaptic structures in the motor cortex as it can regulate the dosage of gene expression *via* homeostatic control of DNA methylation. The over-expression of MeCP2, for instance, resulted in altered structural plasticity of cortical dendritic spines[64]. On the other hand, the deficiency of MeCP2 led to remarkably shorter dendrites of PNs in the motor cortex in human patients across different age groups[38]. Similar phenotypes were observed in mouse models, which presented reduced spine density, shorter dendrite lengths[37], irregular spine clustering or shapes[65] and reduced dendritic complexity[39]. Such evidence clearly demonstrates the relationship between MeCP2 and synaptic plasticity and implies the participation of MeCP2-mediated synaptic defects in Rett syndrome.

Besides the excitatory neurons, GABAergic inhibitory neurons in the motor cortex also tightly regulates motor coordination and motor learning functions, as they can provide both inhibitory synaptic inputs and subthreshold oscillation wave onto excitatory neurons. For example, the somatostatin (SST)-interneuron is found to actively participate in the acquisition and retrieval of complex motor skills as suggested by an *in vivo* recording study[66], and our recent work has revealed the abnormally

suppressed activity of those SST-interneurons under a Parkinson's disease (PD) mouse model, leading to pathologically over-excitation of pyramidal cells[67]. Such phenomena revealed cortical dysfunctions due to the loss of normal inhibitory inputs onto the pyramidal projecting neurons, leading to their hyperactivation and related neural symptoms. Besides the local regulation of cortical inhibition, GABAergic neurons received inputs from subcortical nuclei which consisted of multiple monoaminergic systems. For instance, the α2A -adrenoceptor was found to suppress the activity of cortical inhibitory neurons[68]. The dopamine receptor D1 and D2 have been known to affect the density of cortical inhibitory neurons, including PV- and SST-interneurons[69]. In the human motor cortex, serotonin was also reported to enhance GABAergic transmission[70]. No direct study, however, has investigated the modulation of cortical inhibitory neurons by the monoaminergic system under MeCP2 deficiency. Further work thus can be performed to dissect the circuitry pathway of MeCP2 in affecting motor learning functions.

When one broadens their scope of neurological diseases, it is interesting to find that the "cortical disinhibition" model can be found across different neurological disease models such as Alzheimer's disease (AD)[71], amyotrophic lateral sclerosis (ALS)[72] and Huntington's disease (HD)[73]. In a primate model of Rett syndrome, MeCP2 is expressed in both excitatory and inhibitory neurons in cortical regions[74], implying the possible role for mediating glutamatergic and GABAergic transmission. In specific, the conditional knockout of MeCP2 in cortical vasoactive intestinal peptide (VIP)-interneurons resulted in the deficits of social and mental functions[75]. It thus seems that the abovementioned correlation between MeCP2 and motor function may reside in the inhibitory neurons of the motor cortex. In fact, the cellular pathological studies have also attributed motor dysfunction to MeCP2 deficiency in PV-interneurons in the motor cortex as suggested by a conditional gene knockout model[76]. In a similar manner, the deletion of MeCP2 in SST-interneurons resulted in stereotypic and repetitive behaviors, highlighting the distinct functions of interneuron subtypes in fine motor control [76]. On the other hand, PNs may also be affected under MeCP2 deficits which can impair the structural or functional integrity of the excitatory synapse[11,38,42]. For example, MeCP2 deletion in glutamatergic neurons resulted in much more severe symptoms than those from inhibitory neuron-specific deletion[77]. As the restoration of MeCP2 in GABAergic neurons only partially rescued symptoms in null knockout mice[78], the integrity of local E/I homeostasis is of critical importance for relieving cortical neuropathology in Rett syndrome. Combining all data, it is promising that targeting the E/I balance in the motor cortex, especially by potentiating the inhibitory transmission, may aid in retarding or alleviating the motor syndrome in patients.

THE POTENCY OF EXERCISE TRAINING AND NEUROMODULATION IN FUNCTIONAL REHABILITATION

Based on motor deficits and dysregulated neural plasticity of motor circuits upon MeCP2 dysfunction as aforementioned, it is possible that certain neuromodulation approaches targeting circuitry function might help to ameliorate those motor symptoms. As supporting evidence, environmental enrichment helped to relieve the behavioral deficits including motor learning functions in MeCP2 null knockout mice, in addition to the rescue of cortical LTP function[31]. In a clinical trial of Rett syndrome patients under the age of 6 years, the 6-mo environmental enrichment training paradigm improved motor functions[79]. These examples clearly suggested the possibility of environmental intervention in relieving Rett syndrome symptoms.

Physical training, as one widely accepted life-style intervention to facilitate neurogenesis and cognitive functions[80], has been recently demonstrated by our group to improve motor learning abilities *via* stimulating structural and functional plasticity of synapses in mouse motor cortex[81]. Therefore, exercise training may work as one promising approach to relieve motor deficits of Rett syndrome patients. Such a proposal was supported by several clinical reports in which daily activities and rehabilitation helped to maintain motor abilities[82,83] or to prevent functional deterioration[84]. Specifically, a recently published case report found that periodic exercise rehabilitation at 2 years of age helped to maintain normal motor function[82]. Another study recruited 4 girls under the age of 11 years and found that 2-mo treadmill training helped to improve the general body fitness and behavioral scores[84]. Although these preliminary studies only included a small cohort of patients, the potency of physical exercise in early intervention of Rett syndrome-related motor dysfunction can be tested by large-scale clinical trials in the future.

To provide neurobiological evidence for physical exercise, Zoghbi *et al*[85] recently reported the effectiveness of pre-symptomatic training in the mitigation of specific motor impairments using a mouse Rett syndrome model. In particular, exercise training repeatedly activated a specific population of neurons that developed more dendritic arbors and higher excitability to enhance motor function[85]. These data suggested a possibly new intervention strategy by which endurance exercise works to retard the deterioration of motor dysfunctions. When examining the molecular mechanism underlying exercise intervention on Rett syndrome, BDNF upregulation has been reported upon exercise paradigm in both rodent models[86] and human cohorts[87]. At the downstream of BDNF activation, it is worth noting

that physical training boosted the activity of the mechanistic target of rapamycin (mTOR) pathway for improving structural and functional plasticity of dendritic spines in the motor cortex[81]. Since previous knowledge has established the role of mTOR down-regulation upon Mecp2 mutation[88,89] to generate the phenotypes of Rett syndrome[90], it is highly likely that exercise may help to relieve neural dysfunctions *via* moderately stimulating mTOR pathways. As functional evidence, both *in vitro* and *in vivo* data have proved the down-sized neurons across multiple brain regions in mice carrying the A140V mutation of Mecp2, in association with mTOR activity inhibition[88]. On the other hand, human brain samples presented abnormally upregulated mTOR activity under Rett syndrome[91]. Such discrepancy between human patients and animal models may arise from the different mutational sites or distinct disease stages. Nevertheless, the critical role of the mTOR pathway in MeCP2-related dysfunction and the modulatory role of mTOR by exercise training cannot be neglected. This further highlights the promising future of using endurance training for alleviating cellular and behavioral deficits of Rett syndrome.

Currently, few available intervention strategies have been adopted to benefit Rett syndrome patients. Besides the potential usage of exercise training at early stages as aforementioned, non-invasive neuromodulation approaches provide alternative choices for alleviating behavioral deficits. Various methods including electric, magnetic and ultrasound stimulations have been approved as safe means to modulate neural functions, mainly focusing on the cortical region. The application of transcranial magnetic stimulation (TMS) has been accepted to evaluate the excitability and E/I balance of the M1 neural network[53,54], despite relatively small sample sizes. As an alternative neuromodulation approach, transcranial direct current stimulation (tDCS) has recently been tested on Rett syndrome patients. In one study recruiting 31 patients, tDCS effectively improved attention and verbal functions [92]. A second study also reported enhancement of language skills by tDCS[93]. These neuromodulation approaches thus may have potential values in improving neural functions. Due to the early-onset and persistency of motor deficits, the targeted intervention on the motor cortex may be worth further testing by employing large-scale and multi-centered clinical trials. When considering neuromodulation in large cohorts of patients, however, some concerns may arise as it may result in episodes of epilepsy[94], whose susceptibility rises in Rett syndrome patients[95]. These safety issues also remind that environmental intervention such as exercise training might be a more preferrable and safer way in treating Rett syndrome.

CONCLUSION

In summary, MeCP2 mediates the synaptic plasticity and neural circuitry in the motor cortex and its genetic mutation leads to the disruption of neural transmission, thereby causing the dysfunction of fine motor coordination and motor learning abilities in Rett syndrome. Targeting the motor cortex by either physical training or neuromodulation approaches thus have become accessible and promising strategies for alleviating motor symptoms in Rett syndrome and is worth of more investigations from both basic science and the clinical fields.

FOOTNOTES

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