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Hypothesis

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Early intervention with psychostimulants or antidepressants to increase *methyl-CpG-binding protein 2 (MeCP2)* expressions: A potential therapy for Rett syndrome

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Summary

Rett syndrome (RTT) is a severe X-linked postnatal neurodevelopmental disorder. The syndrome is caused primarily by mutations in the methyl CpG binding protein 2 (*MeCP2*) gene on Xq28. Most individuals with RTT are female, and female RTT is normally heterozygous for mutations in *MeCP2*. Patients with RTT display a normal period of development prior to the onset of symptoms, at which point they undergo a period of regression. Currently, no effective medication is available for this disorder, although animal studies have suggested that RTT symptoms are potentially reversible. For females with RTT, the severity of symptoms and progression of the disease varies a great deal, despite its homogenous genetic origin. These differences could be attributed to differences in the mutation points of *MeCP2* and the skew caused by X-chromosome inactivation. Thus, the increased expression in the normal *MeCP2* gene could decrease the severity of the disease. Based on findings from studies on animals indicating that fluoxetine (an antidepressant) and cocaine (a psychostimulant) can increase *MeCP2* expression in the brain, it is suggested that early intervention with antidepressants or psychostimulants could increase the normal *MeCP2* expression in females with RTT, who are normally heterozygous. This therapeutic hypothesis could be tested in an RTT animal model. Following the identification of the antidepressants or psychostimulants with the greatest influence on *MeCP2* expression, a combination of early detection of the disorder with early intervention may result in improved therapeutic outcomes. Furthermore, a trial investigating the effects of antidepressants or psychostimulants on *MeCP2* expression in lymphocyte culture from patients with RTT is suggested for clinical therapeutic prediction.

key words: **X-chromosome inactivation • *methyl CpG binding protein 2 (MeCP2)* • psychostimulants • antidepressants • treatment • Rett syndrome**

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Background

Rett syndrome (RTT; OMIM # 312750) is a severe X-linked neurodevelopmental disorder in which most patients develop loss-of-function mutations in the *methyl-CpG-binding protein 2* (*MeCP2*) gene [1]. Babies with RTT are generally born after a normal pregnancy and delivery. Most grow and behave normally for the first 6 months, achieving expected milestones in motor, language and social skills. After 6 months, signs and symptoms begin to appear, including cognitive impairment, autistic features such as reduced communication and diminished eye contact, loss of normal movement and coordination, seizures, exaggerated responses to stress and severe respiratory dysfunction [2]. During the latter part of their lives, people with RTT experience impaired motor performance. Life span varies among patients with RTT.

The basic pathophysiology of RTT is considered as deficiency of the activities of the serotonin (5-TH) and the noradrenaline (NA) neurons, which have roles of neuronal development in infancy from 4 months to 18 months of age [3,4]. Sleep studies in people with RTT also suggested that the behavior in the early infancy is due to the hypofunction of these monoaminergic systems in the brain stem and that in late infancy to early childhood, dopaminergic dysfunction leads to the characteristic symptoms [3,5]. Restriction of atonia in rapid eye movement (REM) stage from the 4th month of age induces synaptogenesis of the brain and makes possible integrative function of the brain. Thus, the existence of atonia in non-REM stages after the 4th month causes failure to develop controlled and integrated activity of the whole brain [3]. Leakage of atonia of REM stage into non-REM sleep also causes inhibition of all reflex systems, including those of the autonomic nervous system. This can later appear as abnormal respiration [5].

Hypofunction of the 5-HT and NA neurons, which modulate the antigravity activities or postural tone, causes postural hypotonia and failure in locomotion (ie, crawling) in infancy [5]. These processes cause dysfunction of the pedunculopontine nucleus (PPN), and consequently cause inactivation of the dopamine (DA) neurons in the pars compacta of the substantia nigra (SNc) and the ventrategmental area. For the deficiency concerning the DA neuron, abnormalities of MeCP2 are not directly involved. Thus, the decrease of the tyrosine hydroxylase (TH) in the SNc was improved in a neurohistochemical study of a 32-year-old RTT patient who was trained to locomote from early childhood [3]. However, dysfunction of the 5-HT and the NA neurons directly induced by MeCP2 mutation do not improve by the processes.

To date, no successful medical treatment has been established; therefore, current medical intervention is symptomatic. Nonetheless, studies on RTT mouse models have demonstrated disease reversibility, suggesting that the neurological defects in *MeCP2* mutation are not permanent [6]. Furthermore, studies have shown that neural development in the absence of *MeCP2* does not damage neurons irreversibly, suggesting that RTT is not strictly a neurodevelopmental disorder. These findings are in line with earlier reports indicating that *MeCP2* is required to stabilize the functional state of mature brains, in addition to its role in neurological development [7].

In this report, we propose that early intervention with psychostimulants or antidepressants may increase *MeCP2* gene expression, providing the possibility of treatment for RTT.

Hypothesis

Rett syndrome mainly affects girls with heterozygous mutation in *MeCP2,* as most hemizygous males, as well as homozygous females, do not survive. For females with RTT, the severity of the symptoms and the progression of the disease can vary greatly despite a homogenous genetic origin (*MeCP2* mutation). For example, Auranen et al. demonstrated that atypical and classical RTT can be caused by the same mutations in *MeCP2*, indicating clinical phenotypes are variable even among girls with the same *MeCP2* mutation [8]. One possible cause for the phenotypic variability among RTT patients is the different mutation points in *MeCP2* [9]. Studies have shown that truncating mutations in proximal portions of the *MeCP2* gene are more likely to lead to disorders with a higher degree of severity [10]. Another explanation for the discrepancy in clinical manifestations of RTT is that, in heterozygous females with RTT, X-linked genes are subjected to X-chromosome inactivation (XCI), where 1 of the 2 X-chromosomes are randomly inactivated in every cell of the body. Studies have found that girls with RTT exhibit mosaic expression of the *MeCP2* defect at the cellular level, with most patients showing random XCI and similar numbers of cells expressing the normal *MeCP2* gene and the mutated *MeCP2* gene [8,11]. In a RTT mouse model, it was found that females exhibited a high degree of phenotypic variability beyond what is observed in human patients with similar mutations [12]. X-chromosome inactivation influences the phenotypical outcome of *Mecp2* mutation in mice, in which fewer phenotypes are observed, when a large percentage of neurons have the mutant X-chromosome inactivated [12]. From these findings, and the fact that females with RTT are normally heterozygous for a mutation in *MeCP2,* the increase in the *MeCP2* expression from the normal *MeCP2* gene may help to alleviate RTT symptoms. In studies of normal adult rats, Mecp2 proteins were induced to a significant degree in the brain after 10 days of repeated injections of fluoxetine (an antidepressant) or cocaine (a psychostimulant) [13]. Using real-time reverse transcription polymerase chain reaction experiments, *Mecp2* transcripts were found to be induced by fluoxetine [13]. The potential application of antidepressants for RTT has been suggested, because antidepressants have the potential to increase the production of brain-derived neurotrophic factor (BDNF), which is beneficial in combating RTT [14]. Furthermore, fluoxetine and cocaine are 5-HT elevating agents [15] and 5-HT signaling may enhance gene silencing in postmitotic neurons. Desipramine, a tricyclic antidepressant drug, which inhibits the reuptake of norepinephrine and to a lesser extent serotonin, has been reported to produce beneficial effects on animals with RTT when the agent was administered orally in drinking water [16] or through daily injections [17]. The benefits have been attributed to the noradrenergic activation [16,17]. Desipramine, by blocking the reuptake of NA, strengthens its synaptic effects. These can improve the breathing symptoms by preventing the leakage of atonia of RTT stage and also improve the dysfunction of the DA neuron by activation of the PPN. However, evidence from Cassel et al. [13] suggests that the increase

in *MeCP2* expression could be the primary mechanism underlying the therapeutic effect of antidepressants on RTT.

Several points are suggested for the potential use of psychostimulants or antidepressants in the treatment of RTT:

- First, the effects of psychostimulants or antidepressants on increases in brain *Mecpt2* expression were examined in adult rats [13]. Whether these agents have a similar effect on young animals needs further confirmation. Furthermore, a wide range of psychostimulants and antidepressants are available. Determining which agents have the greatest potential to increase central *MeCP2* awaits further clarification.

- Second, the therapeutic effects of psychostimulants or antidepressants on subjects with RTT could be evaluated in RTT animal models such as conditional *Mecpt2* KO mice, which could provide new strategies for the treatment of this devastating disease.

- Third, RTT is chiefly a neurodevelopmental disorder. Early identification of biological markers or clinical symptoms and signs leading to earlier intervention with psychostimulants or antidepressants may result in improved outcomes. For example, studying family home videos taken prior to regression have identified a number of preregression abnormalities such as hypotonia, jerky incoordination, an excess of patting or waving activity, and involuntary movements among people with RTT [18].

- Fourth, antidepressants can increase brain BDNF, which could provide therapeutic benefits for RTT [14]. Thus, the dual effect of antidepressants (increased BDNF and *MeCP2*) may be superior to psychostimulants in the treatment of RTT.

- Fifth, the mechanisms underlying increases in the expression of *MeCP2* by antidepressants or psychostimulants remain unclear. It will be necessary to determine whether a combination of both agents could have an enhanced effect on *MeCP2* expression.

- Finally, Krepischi et al. noted an increased frequency of skewed XCI in the peripheral lymphocyte of females with RTT, compared with the control group in their study [19]. Considering the fact that treatment with psychostimulants or antidepressants may increase the *MeCP2* expression from the normal X-chromosome, it is anticipated that patients with XCI skewed to a lesser degree would have a better therapeutic response. In addition, the application of psychostimulants or antidepressants to the lymphocyte culture of people with RTT to evaluate the *MeCP2* expression may help to predict therapeutic responses.

Conflicts of Interests

There are no conflicts of interests to report.

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