Published in final edited form as:

Future Neurol. 2013 January 1; 8(1): . doi:10.2217/fnl.12.79.

Recent Progress in Rett Syndrome and MeCP2 Dysfunction: Assessment of Potential Treatment Options

Christopher A. Chapleau¹, Jane Lane², Jennifer Larimore³, Wei Li¹, Lucas Pozzo-Miller¹,
and Alan K. Percy^{1,2}

¹Department of Neurobiology, Civitan International Research Center, The University of Alabama at Birmingham, Birmingham, AL 35294, USA

²Department of Pediatrics, Civitan International Research Center, The University of Alabama at Birmingham, Birmingham, AL 35294, USA

³Biology Department and Neuroscience Program, Agnes Scott College, Decatur, GA 30030

Abstract

Synaptic communication is highly regulated process of contact between cells allowing information to be stored and modified. Synaptic formation and maturation is the result of interactions between intrinsic genetic/molecular factors and the external environment to establish the communication in the brain. One disorder associated with faulty synapse communication is Rett Syndrome (RTT). RTT is the leading form of severe MR in females, affecting approximately 1:10,000 females worldwide, without predisposition to any particular racial or ethnic group. Mutations in *MECP2*, the gene encoding methyl-CpG-binding protein-2, have been identified in more than 95% of individuals with RTT. Birth and the milestones of early development appear to be normal in individuals with RTT until approximately 6–18 months when in the subsequent months and years that follows, physical, motor, and social-cognitive development enter a period of regression. The clinical management of these individuals is extremely multifaceted, relying on collaborations of specialists and researchers from many different fields. In this critical literature review, we provide an overview of Rett Syndrome, from patient to pathophysiology with a therapeutic summary of clinical trials in RTT and preclinical studies using mouse and cell models of RTT.

Keywords

Rett Syndrome; MeCP2; Neurodevelopmental Disorders; Clinical Trials

Introduction

One neurodevelopmental disorder with a distinctive series of developmental periods is Rett Syndrome (RTT; Online Mendelian Inheritance in Man #312750; <http://www.ncbi.nlm.nih.gov/omim/>). RTT is the leading cause of severe intellectual disability in females, with approximately 1:10,000 females worldwide affected by this disease. RTT was first characterized in mid-1960's by Austrian Pediatrician Dr. Andreas Rett, who in his initial case study reported on a number of girls that he was following in his practice that had the same repetitive hand-washing motion with a similar neurodevelopmental phenotype (Rett 1966). This observation would go unnoticed by the broader medical and research community due in large part to the publication of the manuscript in a German-language

medical journal. It was not until the early 1980's when Swedish child neurologist Dr. Bengt Hagberg and colleagues reported 35 females that had a similar disease progression; disease onset around 7 to 18 months of age, with developmental stagnation followed by rapid worsening of neurological functions (Hagberg, Aicardi et al. 1983).

Mutations in a specific gene are not definitive for the diagnosis of RTT, however in an overwhelming majority of individuals, mutations in the gene encoding the transcriptional regulator, methyl-CpG-binding protein 2 (*MECP2*), have been confirmed in more than 95% of diagnosed individuals.¹ RTT is typically diagnosed early in the life of a female and based on strict diagnostic criteria that have been extensively established.^{2,3} These criteria are based on the unique disease progression which begins with halted developmental progress after an apparently uneventful first 6–18 months of life (Percy 2002). After development becomes abruptly stagnated, frank regression occurs in growth, motor, language, and social skills that leads to either partial or complete loss of these skills (Percy 2002). The next period of RTT consists of stabilization and recovery of socialization skills by age four to five with persistence into adulthood.

RTT has certain hallmark observable traits that differentiate this disorder from other neurodevelopmental disorders, including autism. The most noticeable observations are a loss of acquired fine and gross motor skills, an inability to engage socially early in age, and the development of stereotypic hand movements, a classical feature of RTT. Other features of RTT include but not limited to the following:

- Anxiety
- Behavioral Issues
- Breathing abnormalities
- Bruxism
- Cold hands and feet
- Gait dysfunction
- Gallbladder and gastrointestinal dysfunction (i.e. constipation, gastroesophageal reflux)
- Osteopenia
- QT interval prolongation
- Seizures
- Scoliosis
- Sleep alterations

RTT is considered an autism spectrum disorder primarily due to females being withdrawn from social contact, a feature that typically subsides by 4 years of age (Percy 2011). However, major anatomical observations set RTT apart from autism. While individuals with autism are typically male and characterized by increased head circumference, RTT occurs almost exclusively in females who experience a period of abnormal head growth deceleration occurring as early as 1.5 months of age (Tarquinio, in press). Furthermore, dendritic arborization and dendritic spine density is reduced in several brain regions including cortex and hippocampus suggesting abnormal neuronal connections.^{4,5,6} Individuals with RTT typically survive into middle age, and current projections estimate they may survive even longer.⁷

Previous Clinical Trials

Therapeutic management for these individuals can be quite complicated when taking into account their specific neurodevelopmental phenotype. In a previous review, we discussed specific aspects of treatment plans that need to be addressed (Chapleau, et al. *Accepted to Current Clinical Pharmacology*). These treatment plans consist of management of certain disease aspects with already accepted FDA approved medication. However, we did not focus on clinical trials that have been previously conducted. For the most part, few clinical trials have been conducted in the RTT population, testing the efficacy of a certain medication on disease outcome. Furthermore, very few results have come from these clinical trials that have provided unquestionable therapeutic recommendations. It should be noted that clinical trials in RTT are difficult. First, if researchers are focusing on the entire disease state and not necessarily focusing on a particular phenotype (i.e., breathing patterns, cardiac conduction, sleep pattern, stereotypic hand behavior) defining and measuring a primary end point in these individuals is a difficult task. Second, variable phenotypic severity is observed in this disorder, thus comparing results from between participants makes data collection and analysis even more complex. In this section of the review, we will briefly focus on published clinical studies. Because great progress has been accomplished in the basic science aspects of RTT, we will conclude this review examining new findings that have been made, focusing on the development of novel pharmacological interventions in experimental preclinical studies.

Clinical trials have examined the use of therapeutic agents in various phenotypes including motor function, cognition and communication skills to name a few. Seizure disorders represent a common phenotype of RTT, with approximately 85% of individuals reporting some type of seizure occurrence during their lifetimes (Glaze). In an earlier report based on cranial ^1H magnetic resonance spectroscopy, glutamate levels were remarkably increased compared to healthy controls (Lan Percy). Studies using genetically engineered mice with a mutant *mecp2* gene found that the hippocampus, an area of the brain known for seizure initiation, was far more hyperexcitable than in wild-type mice (gaston). Thus, control of seizure frequency could have a great impact on a majority of these individuals. An open-label trial on 12 individuals with RTT, demonstrated that patients respond well in terms of seizure frequency and behavioral issues to the anti-epileptic drug, lamotrigine (Stenbom Y, Tonnby B, Hagberg B). While expansion of this study to determine the extent of benefits of lamotrigine is required, this agent has been demonstrated to be highly effective in maintaining seizure control in RTT.

Separate trials have looked at another phenotype, motor behaviors. Bromocriptine, a monoamine receptor agonist, which primarily activates dopamine receptors with minimal activation of serotonin receptors, was previously used in a very small double blind trial (Zappella, 1990). Minor improvements were observed in motor skills, but for the most part no change in disease state was observed. Due to the possible development of potentially harmful side effects of this agent, which include vasospasm, liver dysfunction and pulmonary fibrosis, further studies have not been conducted and continued use has not been promoted. (Percy, Glaze 1994) Another approved drug that was used to determine its effect on motor dysfunction particularly that of periodic breathing, was the opiate antagonist, naltrexone. Trials of naltrexone were primarily based upon previous studies that demonstrated elevated levels of beta-endorphin in cerebrospinal fluid of individuals with RTT (Budden 1990). Thus, finding a drug that diminished the beta-endorphin effect, naltrexone, could be an excellent candidate. The outcome data demonstrated that while breathing patterns improved, naltrexone appeared to diminish motor behavior overall, suggesting an increased rate of disease progression (percy 1994).

Other clinical trials have been conducted in the RTT population to examine the potential use of vitamins, natural products and other nutrient factors on disease state improvement. An open label trial of the amino acid derivate L-carnitine was shown to be beneficial in sleep maintenance and communication ability.⁸ However, other factors that are more critical to RTT dysfunction, such as physical improvement, hand function or in the quality of life were not improved.

An additional set of clinical trials examined the potential effectiveness of the vitamin, folate, on disease progression. Folate supplementation was proposed in the RTT population for a number of reasons. First, analysis of cerebrospinal fluid demonstrated a reduction from reference values of the folate derivative, 5-methyltetrahydrofolate. A further analysis of these findings demonstrated that on average 5-methyltetrahydrofolate was decreased levels, however the subset that had reduced levels were those patients with a history of epilepsy (Ormazabal A, Artuch R, Vilaseca MA, Aracil A, Pineda M). A second rationale for establishing the effectiveness of folate was molecular genetic pathology of RTT. As discussed in more detail later, MeCP2 is a transcriptional modulator that can alter gene expression epigenetically via methylation of DNA. Thus, another purpose behind the proposed mechanism of action of folate was its ability to methylate segments of DNA (Robert A Jacob), thereby making the mutated MeCP2 protein more capable to bind to various DNA methylated regions. As a result, a clinical trial was established that examined the use of folate supplementation on 73 individuals with RTT who were positive for a *MECP2* mutation. Evaluation of treatment was conducted by the analysis of various conditions including objective measurement of breathing, stereotypic hand behavior, motor function, behavioral issues and subjective parent questionnaires. Results from the study demonstrated no major improvement in objective measurements (Percy Glaze). While no improvement in function was observed with the administration of folate, this study was important and instructive in terms of how future clinical trials in RTT should be carried out. The authors of the study noted that it is essential to match participants based on disease severity, age and mutation type. These three factors if not carefully controlled could have great impact on data analysis and could result in potential skewing of results.

MeCP2 Dysfunction and Related Therapies

As mentioned previously, an overwhelming majority of individuals with RTT (>95%) carry a mutation in the gene encoding MeCP2, a nuclear protein encoded by a gene located in chromosome Xq28.⁹ Recent studies have demonstrated that MeCP2 works as a transcription modifier, working with other proteins to alter the function of genomic DNA.^{10,11} Specifically, MeCP2 binds to DNA, where post-translational modifications of the protein regulate its transcriptional control activity.¹² MeCP2 activates and represses a large number of target genes which in effect are controlled in their activity.¹¹ Thus, dysfunction of MeCP2 and the altered expression of one or more of these genes has the potential to contribute to RTT symptomatology.

Two potential therapies stem from these basic properties of MeCP2. The first option revolves around the lifespan of mutant proteins. Transgenic mice were created with a mutation in the methyl binding domain of the MeCP2 protein (T158A), a mutation that is similar to the most common mutation seen in humans, causing a reduction in MeCP2 binding affinity to methylated DNA and reducing the protein's half-life¹³. Finding a therapeutic option that increases the mutant protein's half-life might have beneficial effects. For instance, selective serotonin re-uptake inhibitors (SSRIs) have been shown to increase expression of MeCP2 (REF). Thus, SSRIs might be one option to circumvent the mutation-induced reduction in the protein's half-life, by increasing the protein's expression.

The second potential therapy relates to the location of the *MECP2* gene. MeCP2 is positioned on the X-chromosome and one allele of the gene will be silenced due to X-chromosome inactivation (XCI). Thus in females with RTT, XCI leads to an environment of a mixture of cells expressing the normal allele and cells expressing the mutant allele. XCI should be a random process, where each cell has a 50% chance of expressing either allele. When XCI is randomly distributed in RTT, individuals tend to be more severely affected compared to situations of nonrandom XCI where a greater percentage of cells express the normal allele¹⁴. By taking advantage of this process, if the normal allele is turned on and the mutant allele is turned off, it is possible that symptom improvement would occur. In an overwhelming majority of instances, *de novo* *MECP2* mutations have been identified in the paternal X chromosome.¹⁵ If this is the case, by identifying the locus of the mutation, a practical approach could be developed to turn off the mutant allele and activate the normal allele. This is a technically challenging, but potentially exciting strategy.

If simply turning one allele off and turning another one on is a potential treatment approach, it should be noted that symptom resolution has already been conducted in transgenic mice. Using an insertion of the *lox-stop* cassette into the *Mecp2* gene of mice, where tamoxifen administration removed the stop cassette causing *Mecp2* expression to be activated fully, symptomatic mice were noted to have markedly diminished severity of RTT-like phenotypes.¹⁶ (Cobbs new paper)

Glia and Glutamate

An exciting recent finding has altered the definition of how RTT is viewed concerning what brain cells express MeCP2. Initially, it was regarded as 'common knowledge' that MeCP2 was a neuron-specific expression protein. However, new data has demonstrated that MeCP2 might also be expressed on non-neuronal brain cells (i.e., oligodendroglia and astrocytes), and that altered expression of MeCP2 in these cells might have extremely deleterious effects on neuronal functions. (Ballas et al., 2009; Maezawa et al., 2009; Maezawa and Jin, 2010) Astrocytes from mutant *Mecp2* mice co-cultured with wild-type neurons caused significant dendritic damage to the neurons. These studies speculated that some toxic factor must be released from mutant astrocytes. One factor already known to be of great importance to RTT is glutamate.

Since glutamate levels tend to be increased in RTT (PerCY), it was not of much surprise to find that MeCP2 in astrocytes modulates the clearance of glutamate (ref). Thus, it is a possibility that abnormally high levels of glutamate could hinder dendritic shape and synaptic number. Recent studies using hippocampal slices from *mecp2* mutant mice demonstrate these tissues to be extremely hyperexcitable (Gaston). This study suggests that modulating glutamate transmission is a possible way to reduce network hyperexcitability. While preclinical trials have not tested the result of reducing glutamate transmission on the overall phenotype presentation in *mecp2* mutant mice, it has been demonstrated that application of the weak NMDA receptor blocker, memantine, restored two short-term plasticity components, post-tetanic potentiation and paired-pulse facilitation. These data suggest that the functional implication of increased glutamate levels needs careful consideration in preclinical trials (Cobb).

Insulin-like Growth Factor-1

A current clinical trial has started revolves around Insulin-like growth factor-1 (IGF-1). IGF-1 is able to penetrate the blood brain barrier, and furthermore is able to stimulate proliferation of neural progenitors, neuronal survival, neurite outgrowth, and synapse formation.^{17,18} To date, a full-length synthetic analog of the IGF-1 molecule is currently FDA approved for the treatment of growth failure in children, and is currently being studied

in an early stage clinical trial to determine side effect profile and disease improvements in RTT ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01253317) identifier: NCT01253317). The initiation of this trial is based on preclinical trials using the tri-peptide fragment of IGF-1 which noted improved motor function, dendritic spine density and motility, and breathing rhythm, in *Mecp2* mutant mice.^{19, 20} Furthermore, IGF-1 increased synapse number in neurons differentiated from iPSCs (induced pluripotent stem cells) reprogrammed from skin fibroblasts of individuals with RTT.²¹

PreClinical Trials: BDNF and Aminoglycosides-Like Compounds

The topics that we have discussed for the treatment of RTT, have for the most part utilized agents that already have some type of FDA approval. However, this section will briefly discuss two additional agents, which while not FDA approved, have shown great promise in the laboratory in the treatment of RTT. A recent finding has added additional light on a class of molecule that has been used by infectious disease experts for years. Aminoglycosides have the capability to read-through premature STOP codons in mutant genes (also known as nonsense mutations) making this class of compounds potentially useful as a pharmacological approach to overcome premature transcriptional termination, a type of mutation that occurs in approximately 35% of North American individuals with RTT.^{22,23} In various models, the full-length MeCP2 protein was discovered in various cell cultures expressing nonsense mutations after incubation with an aminoglycoside antibiotic.^{24,25,26} From a functional standpoint, iPSC-derived neurons from RTT patients expressing nonsense mutations, when treatment with the aminoglycoside gentamicin was employed, demonstrated increased dendritic spine density.²¹ While a potentially useful molecule has yet to be tested in transgenic mouse expressing a nonsense MeCP2 protein, this particular approach might be of great hope for this subset of the RTT population.

Another molecule that has received a great deal of attention has been brain-derived neurotrophic factor (BDNF), a molecule that has been shown to have a substantial role in neuronal survival and synaptic plasticity. In 2003, two high profile research papers demonstrated that MeCP2 regulated the expression of the *Bdnf* gene (ref). Furthermore, low levels of BDNF expression were seen in autopsy brain samples of RTT patients (Deng et al., 2007) and in *Mecp2* mutant mice (Chang et al., 2006; Wang et al., 2006; Abuhatzira, et al., 2007). In addition to low overall levels of BDNF protein, BDNF intracellular trafficking may also been disrupted, as severity and course of characteristic RTT symptoms were correlated with patients carrying BDNF Val66Met polymorphism that is known to impede BDNF maturation process (Zeev et al., 2009).

In recent years, more genetic, physiological and pharmacological manipulations have been developed to attempt to restore normal BDNF levels in RTT animal model and patients, and some beneficial effects have been observed. In mice with *Mecp2* knockdown, *Bdnf* overexpression prevented reduced neuronal growth and arborization (Larimore et al., 2009). Exogenous BDNF application rescued aberrant synaptic function in brainstem nucleus tractus solitarius, which accounts for cardiorespiratory instability in RTT (Kline et al., 2010). Given that BDNF is a molecule with short-life and low blood-brain barrier permeability, physiological intervention such as environmental enrichment, which has been known to promote endogenous BDNF, were utilized, and it was found to ameliorate several RTT-like symptoms including impaired motor coordination and learning (Kondo et al., 2008; Lonetti et al., 2010). Ampakine CX 546 treatment increased BDNF levels in the nodose cranial sensory ganglia, leading to an improvement in respiratory frequency in *Mecp2* mutant mice (Ogier et al., 2007). Similarly, respiratory frequency in mutant mice was recovered by a small analog of BDNF that can be administered systemically and activate the TrkB receptor (Schmid et al., 2012).

Especially intriguing was a paper that was published a few years later that demonstrated that BDNF protein levels were found to be lower in brain samples of *Mecp2* mutant mice, a result that was also discovered by assessing mRNA levels in human RTT brain.^{27,28} From these three seminal papers, researchers began to examine how BDNF could be used on the treatment of RTT.

A number of approaches used to activate or mimic BDNF, has been shown to be useful in RTT preclinical studies. *BDNF* overexpression in *Mecp2* mutant mice or in neurons transfected with RTT-associated *MECP2* mutations reversed behavioral phenotypes in animals and dendritic atrophy in primary neuron cultures, respectively.^{27,29} Furthermore, molecules that act like BDNF, called “BDNF mimetics”, that have the capability to pass through the blood brain barrier (BBB) and bind to TrkB receptor have proven useful in attenuating disease progression. TrkB agonists, LM22A-4 and 7,8-dihydroxyflavone (7,8-DHF), have shown promise to reverse RTT-like features in experimental mouse models.^{30,31} Because of the pharmacokinetic properties of BDNF, which causes rapid break down and the inability to pass the blood–brain barrier, these molecules offer hope of targeting BDNF. However, much research still needs to be conducted to prove the safety and efficacy of this class of drugs both in animal models and in humans.

Conclusions

Research into the clinical management of RTT relies on focusing on present day treatment using FDA approved agents and future research using newly found molecules. Moreover, the present day treatment research focuses on reviewing the entire spectrum of symptoms that relate to RTT, while future treatment options focus on discovering molecules that cure the entire disorder. Since MeCP2 activates and represses a large number of target genes, dysfunction in the expression of these genes could contribute to RTT symptomatology. Thus, research into the treatment of RTT, must rely on determining which deregulated genes contribute to a specific symptom or symptom cluster, and what drug therapy might overcome these dysfunction.

While mutations in MeCP2 are highly correlated with the diagnosis of RTT, the specific functions of MeCP2 that are impaired by mutations and are responsible for RTT symptomatology remain a mystery. Further research examining MeCP2 dysfunction needs to examine the influence of MeCP2 mutations on other disorders. The association of MeCP2 mutations in other disorders has also been documented (ref). For example, mutations of MeCP2 have been linked to schizophrenia. A case report published 10 years ago, described of a 12-year-old boy with a mutation of MeCP2, diagnosed with a developmental disorder, in addition to childhood-onset schizophrenia³². Recent insight into genes regulated by MeCP2 indicates an overlap with genes altered in schizophrenia. A cluster of the genes found altered in both schizophrenia and RTT code for proteins that regulate neuronal endosomal trafficking (Zhogbi 2008). Thus, understanding the dysfunction of MeCP2 mutations and the dysregulated genes that contribute to specific symptoms will be helpful to understanding the molecular mechanisms that have failed in both RTT and schizophrenia in addition to other disease where MeCP2 mutations have occurred.

Acknowledgments

Supported by grants from NIH-NINDS (NS40593, NS057780, NS065027 to LP-M) and NIH-NICHD (U54 grant HD061222 and IDDRC grant HD38985 to AKP), the International Rett Syndrome Foundation, and the Civitan International Foundation.

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