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Rett's syndrome

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CONTENTS

Abstract

Rett's syndrome is a progressive neurodevelopmental disorder with childhood onset that almost exclusively affects females. Patients with Rett's syndrome are severely disabled and highly dependent on others for their daily activities due to profound cognitive and motor deficits. Despite striking advances in the identification of the molecular and genetic mechanisms underlying this disorder, there is no cure for Rett's syndrome and current therapies are mainly aimed at alleviating the symptoms. Correlations between genotype and clinical phenotype would help to develop targeted therapies. In this article, we summarize the molecular pathogenesis of Rett's syndrome and present current and future treatment approaches.

Introduction

Rett's syndrome is a severe, pervasive neurodevelopmental disorder predominantly affecting young girls. It is a relatively common condition (estimated prevalence 1:10,000) characterized by normal development for the first 6-18 months of age, followed by a phase of developmental stagnation (stage I), which progresses to a period of regression (stage II). Deceleration of head growth, loss of motor skills, reduced social interaction and stereotypic hand movements occurring after the loss of purposeful hand function are some of the features that delineate this disorder. At the late stages (stage III-IV), severe growth retardation, seizures, aggravated motor problems and scoliosis are typical (1, 2). Rett's syndrome is caused by mutations in the X-linked gene encoding methyl-CpG-binding protein 2 (MeCP2), although more recently mutations in the cyclin-dependent kinase-like 5 (*CDKL5*) and netrin G1 (*NTNG1*) genes have also been associated with a Rett's-like phenotype (2).

The genetics of Rett's syndrome

The MECP2 gene

The *MECP2* gene is located on the X chromosome (Xq28 locus) and selectively binds CpG dinucleotides in the genome via its methyl-binding domain. It then mediates gene transcription repression through other proteins recruited by its transcription repression domain. MeCP2 has been suggested to play a role in controlling the expression of genes involved in neuronal maturation (2). *MECP2* is subject to X chromosome inactivation, which in females results in mosaics of cells with normal or defective MeCP2 activity. This pattern of X chromosome inactivation yields a variety of phenotypes in females that range from asymptomatic (mutation carriers) or mild learning disability or autism to more severe cases of mental retardation with seizures or Rett's syndrome. Typically, Rett's syndrome features random X chromosome inactivation, with about 50% of cells expressing the mutated MeCP2 (1, 4). In males, total deletion of *MECP2* in their only X chromosome leads to more severe phenotypes that include epileptic encephalopathy, apnea and death within the first 2 years of life, although the classic Rett's syndrome phenotype may also occur (3). The *MECP2* gene comprises four exons, with mutations occurring predominantly in exon 3, which comprise missense, nonsense (truncating) and frameshift mutations. Both factors, mutation type and X chromosome inactivation pattern, account for the diversity of the clinical manifestations observed (1, 4).

Although the exact function of MeCP2 has yet to be clarified, increasing evidence from animal models of Rett's syndrome and humans supports a role in neuronal development and synaptic plasticity. The MeCP2 protein expression pattern has been found to correlate with central nervous system (CNS) maturation in humans and mice, being expressed first in the spinal cord and lastly in the cerebral cortex. In human cortex, MeCP2 expression is initiated in Cajal-Retzius cells, followed by deeper cortical neurons and finally by the more superficial layers (5). This pattern of expression may explain the delayed onset of symptoms in Rett's syndrome, typically between 6 and 18 months of age, when a certain degree of CNS maturation has already been reached (6).

Mouse models of the disease have contributed to a better knowledge of MeCP2 function. Total deletion of *Mecp2* is highly deleterious for these animals, which pre-

sent normal development initially, followed by progressive neurological impairment and death at 7-10 weeks. In addition, *Mecp2* knockout mice show a delay in olfactory neuron differentiation and small pyramidal neurons with thinner connections and poorly developed cortical dendritic arbors, indicating a role for MeCP2 in neuronal development and potentially in synapse development (7). Interestingly, transgenic MeCP2 expression in *Mecp2*-null mice was able to reverse the Rett's syndrome phenotype typically exhibited by these animals (8), whereas MeCP2 protein overexpression is known to cause progressive neurological impairment (7). In mice bearing an MeCP2 protein truncated at amino acid 308, known as MecP2^{308}, the clinical phenotype is milder because it preserves enough of the protein for mice to be viable. Although cortical and hippocampal neuronal morphology is preserved, these animals present with deficits in spatial and hippocampus-dependent memory and impaired synaptic plasticity (9). In addition, *MECP2* gene duplication has been associated with Rett's-like syndrome and mental retardation in males (7). Consequently, gene therapy may not be advisable for treating this disorder, as gain- and loss-of-function mutations share similar phenotypes.

The CDKL5 gene

Mutations in the *CDKL5* gene have been identified in patients exhibiting different clinical phenotypes from early-onset seizures to mental retardation (10). Interestingly, Cdkl5 and MeCP2 present significantly similar spatial and time expression patterns, with increased protein levels as neuronal maturation progresses, which indicates a convergence of both proteins in the same molecular pathway. In addition, Cdkl5 appears to mediate MeCP2 phosphorylation (*i.e.,* activation of *BDNF* gene transcription), although it remains to be determined whether MeCP2 is the direct target of Cdkl5 (11). Nevertheless, disease-causing mutations in *CDKL5* can impair MeCP2 phosphorylation, which may contribute to the pathogenesis of Rett's syndrome (12).

The NTNG1 gene

The *NTNG1* gene plays an important role in CNS development, particularly in axon guidance. Although *NTNG1* mutation was found to be associated with Rett's syndrome in 1 case (2), recent investigations have failed to identify pathogenic mutations in *NTNG1* in Rett's syndrome patients negative for *MECP2* mutations (13).

Potential MeCP2 target genes

The BDNF gene

One of the target genes of MeCP2 is the gene encoding for brain-derived neurotrophic factor (BDNF), known to play a role in neuronal development, survival and synaptic plasticity (7). In the absence of neuronal activity, MeCP2 binds to the *BDNF* promoter to repress the expression of the *BDNF* gene. However, neuronal membrane depolarization triggers calcium-dependent MeCP2 phosphorylation (at serine 421) and subsequent release from the *BDNF* promoter, thus inducing gene transcription (14, 15). Dendritic and spine morphogenesis and maturation are also mediated by activity-dependent induction of *BDNF* transcription (15).

But what role does BDNF play in the pathogenesis of Rett's syndrome? A recent study demonstrated that BDNF protein levels are reduced in *Mecp2* mutant mice and that *Bdnf* gene deletion leads to an earlier onset of Rett's syndrome in these animals, whereas *Bdnf* overexpression in *Mecp2* mutants delayed the onset of Rett's symptoms and improved impaired locomotor function, thus modulating disease progression (16). *Mecp2* deletion is correlated with decreased cortical activity (16, 17), which may explain decreased BDNF expression, as its transcription is dependent on neuronal activity. Recent research has unveiled transient receptor potential (TRP) channels as novel downstream targets for BDNF, with a subsequent putative role in the pathogenesis of Rett's syndrome (18). According to this hypothesis, BDNF may trigger TRP channel-mediated capacitative calcium entry, thus initiating calcium signaling cascades that may be necessary for the induction of synaptic plasticity and dendritic spine remodeling.

The use of drugs that increase central BDNF levels as potential treatments for Rett's syndrome has therefore been proposed. Semax (ACTH[4-7]-PGP) is a nonhormonal analogue of the *N*-terminal fragment of adrenocorticotropic hormone that has been shown to increase BDNF synthesis in primary glial cell cultures and in the rat hippocampus and nasal forebrain upon nasal application *in vivo* (19). Chronic treatment with zinc sulfate, lithium or antidepressants has also been associated with elevated BDNF levels (20, 21) and may be of use in Rett's syndrome.

Other genes

Four members of a transcriptional regulator family called inhibitors of differentiation (ID1, ID2, ID3 and ID4), which block the function of basic helix-loop-helix (bHLH) genes, have recently been identified as targets of MeCP2 (22). bHLH genes control cell growth and differentiation in many cell types, including neurons in the peripheral and central nervous system. MeCP2 was found to bind to ID1, ID2 and ID3 promoters and the expression of all ID genes was elevated in the brain of *Mecp2*-null mice and Rett's syndrome patients, which may indicate a the role for MeCP2 as a repressor of genes controlling maturation and differentiation. Increased ID expression may translate into poor expression of bHLH proteins, thus compromising neuronal differentiation (22).

More recently, investigations in *Mecp2^{308}* mutant male (*Mecp2$^{308/Y}$*) mice disclosed the corticotropin-releasing hormone (*Crh*) gene as a novel MeCP2 target (23). In this mouse model of Rett's syndrome, *Crh* overexpression in the paraventricular nucleus of the hypothalamus, togeth-

er with enhanced anxiety-like behavior and an abnormal corticosterone response to stress, indicated a potential role in the development of anxiety behavior in Rett's syndrome patients. MeCP2 was found to modulate *Crh* transcription in wild-type mice, whereas this was impaired in *Mecp2*$^{308/Y}$ mice, which resulted in enhanced CRH expression.

Management of Rett's syndrome

There is currently no cure for Rett's syndrome and treatment of this disorder is symptomatic and geared towards maximizing patient abilities. Therapeutic interventions are varied and depend on the clinical picture presented by each patient. A multidisciplinary approach is often taken, with physical and occupational therapy to improve the child's mobility. Relevant clinical studies are summarized in Table I.

Neurological disorders

Epilepsy occurs frequently in Rett's syndrome cases. Treatment options range from anticonvulsant drugs, such as carbamazepine or lamotrigine, to nonpharmacological strategies (*i.e.,* vagus nerve stimulation). A recent retrospective study on 110 female patients highlighted the benefit of carbamazepine for seizure control over valproic acid and sulthiame, and recommended it as a first-choice

Table I: Clinical studies of experimental therapies for Rett's syndrome (from Prous Science Integrity®).

Drug/Intervention	Design	Treatments	n	Conclusions/Objectives	Ref.
Neurological disorders					
Antiepileptic drugs	Retrospective	Carbamazepine x 102 mo Valproic acid x 29 mo Sulthiame x 36 mo	110	The antiepileptic efficacy of carbamazepine was found to be superior to valproic acid and sulthiame in a retrospective study of Rett's syndrome patients treated with these agents	24
	Open	Lamotrigine, 0.1-7.5 mg/kg b.i.d. [adjusted to C_{ss} 2-4 µg/ml] p.o. x 12 wks	12	Lamotrigine could be a valuable adjunctive treatment option for patients with Rett's syndrome	25
	Case report	Lamotrigine, 3 mg/kg/d p.o.	2	Lamotrigine successfully controlled seizures and markedly reduced stereotypic hand movements and autistic behavior in 2 children with Rett's syndrome	26
Vagus nerve stimulation	Open	Vagus nerve stimulation x 1 y	7	Vagus nerve stimulation was safe, well tolerated and improved seizure control and alertness in patients with Rett's syndrome	27
Folinic acid	Open	Folinate, 0.5-1.5 mg/kg/d p.o.	16	Folinic acid supplementation improved seizure control in patients with Rett's syndrome and cerebrospinal fluid 5-methyltetrahydrofolate deficiency	28
Baclofen	Case report	Baclofen, 800 [max.] µg/d i.thec. x 1 y	1	Intrathecal baclofen was effective for managing severe spasticity in a woman with Rett's syndrome	29
Dextromethorphan/ donepezil	Open Randomized	Dextromethorphan Donepezil	90	This phase III study will evaluate the efficacy of dextromethorphan and donepezil in treating neurological symptoms in patients with Rett's syndrome	30
Behavioral disorders					
Olanzapine	Case report	Olanzapine, 5 mg b.i.d. + 5 mg x 2 [if severe self-injurious or aggressive behavior]	1	Olanzapine effectively reduced agitation and self-injurious/aggressive behavior in a 16-year-old girl with Rett's syndrome	35
Bromocriptine	Case report	Bromocriptine, 2.5 mg b.i.d. x 3 mo	1	Bromocriptine decreased stereotypic hand movements and motor dysfunction in a 7-year-old girl with Rett's syndrome	36
	Open	Bromocriptine, 1.25 mg p.o. b.i.d. [if ≤ 25 kg] or 2.5 mg p.o. b.i.d. [if > 25 kg] x 6 mo	13	Bromocriptine treatment reduced stereotypic hand activities in 40% of patients with Rett's syndrome, and improvements in communication and relaxation were also observed in some girls	37

Continuation

Table I (Cont.): Clinical studies of experimental therapies for Rett's syndrome (from Prous Science Integrity®).

Drug/Intervention	Design	Treatments	n	Conclusions/Objectives	Ref.
L-Carnitine	Randomized Double-blind Crossover	L-Carnitine, 33.3 mg/kg/d p.o. t.i.d. x 8 wks Placebo	35	L-Carnitine was beneficial for some patients with Rett's syndrome and improved well-being and hand apraxia scale scores. However, no major functional changes were observed	43
Sleep disorders					
Melatonin	Case report	Melatonin, 5-10 mg/d p.o. → ld., 3 mg/d p.o. [bedtime] x 2-3 y [maintenance dose]	2	Melatonin treatment markedly improved the sleep/wake cycle in 1 patient, but although it exerted hypnotic effects in the other patient, it was not effective in treating early-morning awakenings	39
	Case report	Melatonin, 3 mg p.o. o.d. [bedtime]	1	Melatonin improved the sleep/wake cycle and reduced night screaming attacks	40
	Randomized Double-blind Crossover	Melatonin, 2.5-7.5 mg [bedtime] x 4 wks Placebo	9	Melatonin improved total sleep time and efficiency in patients with Rett's syndome, especially in those with worse baseline sleep quality	41
L-Carnitine	Open	L-Carnitine, 50 mg/kg p.o. b.i.d. x 6 mo Control	83	L-Carnitine significantly improved sleep efficiency in patients with Rett's syndrome	43
Pipamperone	Case report	Pipamperone, 8 mg p.o. b.i.d.	1	Pipamperone significantly improved sleep disturbance in a patient with Rett's syndrome	44
Cardiorespiratory dysfunction					
Oxygen therapy	Case report	Carbogen (5% CO_2/95% O_2) inh.	1	CO_2/O_2 inhalation prevented the severe forceful breathing in a patient with Rett's syndrome, thus improving quality of life	44
Buspirone	Case report	Buspirone, 5 mg p.o. b.i.d. x 5 mo	1	Buspirone improved oxygen saturation in a 15-year-old patient with Rett's syndrome presenting respiratory dysfunction associated with late motor deterioration stage (stage IV)	46
Naltrexone	Randomized Double-blind Crossover	Naltrexone x 4 mo Placebo	25	Naltrexone could modify some of the respiratory disturbances associated with Rett's syndrome, but induced deleterious effects on motor function and was associated with more rapid progression of the disorder	48
Acetyl-L-carnitine	Open Randomized	Acetyl-L-carnitine, 50 mg/kg/d x 6 mo Control	22	Acetyl-L-carnitine was found to improve heart rate variability and to moderately reduce sympathetic overactivity in Rett's syndrome patients	52

antiepileptic drug in Rett's syndrome (24). In addition to seizure control, lamotrigine therapy has been shown to improve motor function and overall quality of life. Results from a small open study revealed antiepileptic effects together with increased alertness, concentration and improved general well-being (25). Also, a report of 2 children treated with lamotrigine (3 mg/kg/day) showed a decrease in stereotypic hand movements together with seizure suppression (26).

Vagus nerve stimulation has shown promise in the treatment of Rett's syndrome-associated epilepsy in a recent study, where 6 of 7 patients experienced a reduction in seizure frequency of 50% or more at 1 year of treatment. In addition, vagus nerve stimulation therapy was safe and well tolerated, and improvement in patient quality of life was also reported (27).

A subset of Rett's syndrome patients exhibit 5-methyltetrahydrofolate (5-MTHF) deficiency in cerebrospinal fluid (CSF), which in turn is associated with decreased tetrahydrobiopterin, the main cofactor necessary for serotonin and dopamine biosynthesis. A small study reported that patients with low 5-MTHF levels also presented with seizures that could be controlled with folinic acid supplementation in combination with other antiepileptic drugs (28).

In addition to epilepsy, Rett's syndrome patients experience other neurological symptoms such as spasticity, particularly in late stages of the disease. Spasticity can lead to locomotor disabilities or scoliosis, which interfere significantly with patients' daily activities. In 1 patient, intrathecal baclofen administration for 1 year (up to 800 μg/day) decreased spasticity with concomitant pain

reduction, improvement in body positioning and quality of life (29).

Other treatment approaches to alleviate neurological symptoms in Rett's syndrome include dextromethorphan and donepezil hydrochloride, which will be evaluated in an open, randomized clinical study that is expected to recruit 90 patients (30).

Learning, cognitive and behavioral disorders

As mentioned earlier, learning and memory are impaired in the *Mecp2*$^{308/Y}$ mouse model of Rett's syndrome, with animals showing deficits in spatial and social memory and deficient hippocampal long-term potentiation (LTP) (9). Moreover, *Mecp2* deletion has led to more severe cognitive impairment, likely due to total loss of MeCP2 protein, with mice showing reduced locomotor activity and cerebellar learning. Decreased levels of anxiety and impaired fear conditioning were also found in *Mecp2*-null mice (31).

Antipsychotic drugs have demonstrated some benefit in the treatment of behavioral symptoms of pervasive developmental disorders. For instance, risperidone, a dual antagonist at dopamine D2 and 5-HT_{2A} receptors, was recently approved for the treatment of irritability associated with autistic disorder, including symptoms of aggression towards others, deliberate self-injury, temper tantrums and quickly changing moods, in children and adolescents aged 5-16 years. Although risperidone can relieve behavioral symptoms, such as stereotypy, in children with pervasive developmental disorders (32), its efficacy in Rett's syndrome has not been proven and unpublished observations have associated risperidone with worsening of symptoms (33). Olanzapine is currently undergoing phase II/III studies at the National Institute of Mental Health for the treatment of autism (34). Although, it has been reported to attenuate agitation and self-injurious behavior in an adolescent girl with Rett's syndrome (35), clinical experience with olanzapine has not demonstrated efficacy (33). Bromocriptine, a dopamine D2 receptor antagonist, has been reported to reduce stereotypic hand movements and motor dysfunction, improve sleep patterns and reduce hyperventilation attacks (36, 37). In animal models of partial dopamine depletion induced by GBR-12909, a dopamine reuptake inhibitor, self-injurious behaviors resembling those of Rett's syndrome patients are observed, indicating that dopaminergic dysfunction in the brain basal ganglia may account for aberrant behaviors in Rett's syndrome, providing an *in vivo* model for further study (38).

Sleep disorders

Rett's syndrome patients often experience sleep disorders, with aberrant sleep patterns consisting of decreased nighttime and increased daytime sleep compared to age-matched healthy children. Sleep disorders have been associated with impaired melatonin secretion in these patients, as exogenous melatonin administration improved sleep time and quality in isolated case reports (39, 40). Several authors have correlated the period of developmental regression in Rett's syndrome with deficient maturation of the melatonin secretory system (39). Intriguing observations in mice have also found that in response to light, MeCP2 is phosphorylated in the suprachiasmatic nuclei of the hypothalamus, hence indicating a potential role for MeCP2 in the regulation of the sleep-wake cycle (15).

A double-blind, placebo-controlled clinical study in 9 girls with Rett's syndrome reported improved total sleep time and sleep efficiency after treatment with melatonin, particularly in patients with poor baseline sleep quality (41).

The efficacy of L-carnitine in improving sleep efficiency has also been described (42), although its mechanism of action has not been clarified. A randomized, double-blind, placebo-controlled, crossover clinical study concluded that L-carnitine (100 mg/kg/day) increased patients' general well-being, whereas motor skills remained unaffected (43). The 5-HT_{2A} receptor antagonist pipamperone has been reported to induce sleep and normalize sleep patterns in a girl with Rett's syndrome, and it also helped to improve breathing irregularities (44).

Cardiorespiratory dysfunction

Autonomic nervous system dysregulation underlies cardiorespiratory problems observed in Rett's syndrome patients, who may exhibit breathing irregularities characterized by periods of apnea and/or hyperventilation, usually occurring during waking hours, while normal breathing is preserved during sleep (2). According to breathing patterns of Rett's syndrome patients, three different phenotypes can be identified which could reflect different levels of brain stem immaturity and require adapted clinical management: apneustic, forceful and feeble breathers (45). Administration of the 5-HT_{1A} receptor agonist buspirone (5 mg b.i.d) to a 15-year-old girl with Rett's syndrome with apnea episodes associated with cyanosis improved oxygen saturation and normalized the irregular breathing pattern, which also influenced the patient's behavior by increasing social contact and alertness (46). In fact, *Mecp2* deficiency in mice has been associated with low brain stem serotonin content and abnormal respiratory rhythm (47).

An isolated case report described a Rett's syndrome patient classified as a forceful breather, who experienced severe hypocapnia attacks due to hyperventilation and Valsalva's type of breathing, which were particularly life-threatening as they prompted vacant spells and abnormal brainstem activation involving increased heart rate and blood pressure. Long-term treatment with inhaled carbogen (5% CO_2 and 95% O_2) caused a marked reduction in the hypocapnia attacks by preventing a decrease in blood partial CO_2 pressure, thus significantly improving the patient's quality of life (44).

In contrast, other pharmacological interventions have been of limited success. A double-blind, placebo-con-

trolled, crossover clinical study in patients with Rett's syndrome demonstrated that the opiate antagonist naltrexone was able to improve disorganized breathing patterns, but negatively affected motor function, leading to disease progression (48).

Abnormal breathing patterns, such as recurrent breathholding, have been linked to increased heart rate and blood pressure oscillations and may contribute to sudden death in Rett's syndrome patients (49). Sudden death is a common and serious cardiac condition, with a higher incidence in Rett's syndrome patients compared to the general population (50). Sudden death in these patients has been ascribed to electrocardiographic abnormalities, including prolonged corrected Q-T (QT_c) interval or nonspecific T wave changes. Interestingly, some authors have reported a correlation between prolonged Q-T_c (caused by defective repolarization after ventricular systole) and an age-dependent decline in nerve growth factor (NGF) levels in the plasma of patients with Rett's syndrome and in rats treated with antibodies against NGF (51). Abnormal NGF signaling may lead to abnormal development of heart nexal and desmosomal junctions and deficient cardiac innervation, which could account for the prolonged Q-T_c interval (50). In this context, acetyl-L-carnitine has been shown to improve heart rate variability (usually low in Rett's syndrome and indicative of autonomic dysfunction) and to moderately reduce sympathetic overactivity in Rett's syndrome patients, which may be beneficial for reducing the risk of sudden death (52).

In addition to electrocardiographic findings, a down-regulation of *KCNH2*, which encodes the α-subunit of a voltage-gated potassium channel essential for ventricular repolarization (HERG channel), has also been found in patients with *MECP2* mutations (53).

Future trends

Understanding the relationship between the genetic basis, clinical manifestations and progression of Rett's syndrome is key to develop future targeted therapies. The Office of Rare Diseases at the National Institutes of Health (NIH) and others are currently studying the genotype-phenotype correlations in Rett's syndrome patients positive for an *MECP2* mutation (54).

In addition, a review of the patent literature disclosed current research on different therapeutic approaches to Rett's syndrome. Lilly is investigating the use of norepinephrine reuptake inhibitors (atomoxetine, reboxetine) for the treatment of pervasive developmental disorders including Rett's syndrome (55), as low brainstem levels of norepinephrine in *Mecp2*-deficient mice have been correlated with respiratory disturbances (47).

Although gene therapy is difficult because *MECP2* gene expression is tightly regulated, researchers at Kurume University have investigated the potential therapeutic effect of expression vectors containing an active *Mecp2* gene with promising results. Injection of an adenovirus vector carrying *Mecp2* into the corpus striatum in a murine model of Rett's syndrome (*Mecp2* deficiency) resulted in an improvement in both motor and mental function (56).

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