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Is riluzole a potential therapy for Rett syndrome?

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ABSTRACT

Rett syndrome (RTT) is a severe neurodevelopmental disorder with autistic features and is caused by loss-of-function mutations in the gene encoding methyl-CpG-binding protein 2 (MECP2) in the majority of cases. Besides symptomatic treatment, no therapeutic trials have shown effectiveness for RTT. Some perspectives in the treatment of RTT have been provided by recent works showing a phenotypic reversal by increasing brain-derived neurotrophic factor (BDNF) expression in a RTT mouse model. Glutamate may also play an important role in the primary pathogenesis in Rett syndrome through the excitotoxic neuronal injury in experimental models. Riluzole, an agent currently approved for the treatment of amyotrophic lateral sclerosis, is a glutamatergic modulator and BDNF enhancer with neuroprotective properties. For these reasons, riluzole could potentially play an important role in the treatment of RTT symptoms. Several points regarding the use of riluzole in RTT are discussed. Further evaluation of the therapeutic effects of this agent in RTT animal models is needed before clinical trials can begin.

Introduction

Rett syndrome (RTT; OMIN # 312750) is a postnatal severe and progressive neurodevelopmental disorder occurring almost exclusively in females, and it is one of the most common causes of mental retardation. After 6–18 months of apparently normal development, RTT patients show global deceleration of psychomotor development and subsequent loss of acquired cognitive and motor skills (*e.g.* loss of acquired motor skills and speech). Patients may also develop pathognomonic stereotyped hand movement or display autonomic dysfunction such as breathing irregularities [1]. With intensive care, RTT patients may survive into adulthood, yet they are severely mentally retarded.

RTT is a genetic disease and is caused almost exclusively by mutations in the X-linked gene *MECP2* encoding methyl-CpG-binding protein 2 (MECP2) [2]. MECP2 is a methylated DNA-binding protein, which specifically binds to methylated DNA *in vitro* and represses transcription from methylated promoters [3,4]. With the important role of MECP2 in brain development, clinical studies have shown RTT patients to have a smaller brain volume and alterations in various neurotransmitter systems, including acetylcholine, dopamine, serotonin, glutamate, substance P, and various trophic factors [5].

Although the investigators have made great progress in revealing the RTT pathogenesis, to date, no successful medical treatment has been established; therefore, current medical intervention is symptomatic. Nonetheless, recently some preliminary trials of theoretically potential agents have been reported. For example, irregular breathing is a prominent feature of RTT, and brainstem serotonergic neurons are known to be implicated in breathing rhythm and pattern. A recent study demonstrated that combined buspirone (a serotonergic 1A agonist) and fluoxetine (a selective serotonin reuptake inhibitor) might be helpful in treating respiratory dysfunction associated with RTT [6].

Riluzole is a sodium channel-blocking benzothiazole anticonvulsant drug which is currently approved by the US Food and Drug Administration for the treatment of amyotrophic lateral sclerosis (ALS) [7]. Riluzole seems to be well tolerated in people at the doses used in treating ALS. The most frequent dose-related adverse events include nausea, asthenia, modest elevation of transaminases, especially alanine aminotransferase [8]. The mechanism of action of riluzole in the nervous system is complex and it is presently being used off label in the treatment of psychiatric disorders in adult/children patients, including major depressive disorder, generalized anxiety disorder and obsessive–compulsive disorder [9]. Here, I propose that riluzole, which could modulate glutamate function and increase central brain-derived neurotrophic factor (BDNF) levels, might be potential agent for the treatment of RTT.

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Medical hypothesis

BDNF is a member of the neurotrophic factor family and has been shown to function as a key regulator of neurite outgrowth, synaptic plasticity and neurotransmitter release across multiple neurotransmitter systems in the brain [10]. BDNF utilizes a dual receptor system to modulate diverse and sometimes opposing biological actions that consists of a specific high affinity receptor, tyrosine kinase receptor B, and a common low affinity receptor, p75 neurotrophin receptor [11].

In 2003, *Bdnf* was first identified as a possible neuronal target gene for MECP2; in cultured neonatal cortical neurons [12]. A later report by Chang et al. showed that BDNF protein levels in the whole-brain lysate in *Mecpt2* knockout mice were decreased to about 70% of the wild-type level [13]. Two studies described lower *BDNF* mRNA levels in autopsy brain samples from RTT individuals, which is similar to that found in *Mecp2* mutant mice [14,15]. In the report by Chang et al., it was elegantly demonstrated that deletion of *Bdnf* in *Mecp2* mutants caused an earlier onset of RTT-like symptoms, whereas increased brain BDNF expression in the *Mecp2* mutant extended the lifespan, rescued a locomotor defect, and reversed an electrophysiological deficit [13]. From these findings, the authors suggested that RTT pathogenesis may be partially mediated through BDNF signaling, and therefore improving BDNF expression and/or signaling in brain could be therapeutic for this disease [13]. The important role of BDNF in RTT pathogenesis and symptoms is further supported by genetic studies, which demonstrated that the functional *BDNF* Val66Met polymorphism may affect the onset of the seizures [16] and severity of clinical symptoms in RTT subjects [17].

Improving BDNF expression and/or signaling have received much attention for the treatment of Rett syndrome [18]. *In vitro* study has shown that BDNF overexpression in hippocampal neurons prevents dendritic atrophy caused by Rett-associated *Mecp2* mutations [19]. Since the administration of BDNF is not a useful clinical approach due to its short half-life and low blood–brain barrier penetration, pharmacological manipulations that can increase endogenous BDNF expression or its downstream signaling pathways are more practical for the treatment of RTT. For example, irregular breathing is one of the most typical features in RTT, and BDNF signaling plays an important role in the development and maintenance of synaptic and neuronal function within brainstem respiratory nuclei. The respiratory dysfunction in RTT mouse model as well as RTT individuals is significantly improved by antidepressants, which can increase brain BDNF levels [6,20–22].

In 2001, Mizuta et al. first demonstrated that riluzole stimulates synthesis of BDNF in cultured mouse astrocytes [23], which is in line with clinical study that treatment with riluzole significantly increases serum levels of BDNF in patients [24]. Later animal studies also found that riluzole can enhance brain BDNF expression and exert neuroprotective effects [25–27]. The above findings suggest that riluzole has the potential to treat RTT through increasing brain BDNF function and subsequent neuroprotective effects.

Riluzole has also other effects which may contribute to its therapeutic potential for RTT, including its multiple effects on the N-methyl-D-aspartate receptor (NMDAR)-glutamate system. MeCP2 is a transcriptional repressor which may protect against NMDAR mediated excitotoxicity in neurons, and neurons of RTT patients may be more susceptible to excitotoxicity [28]. Riluzole has been found to inhibit excitotoxic injury in experimental models through direct effects on the glutamatergic system, resulting from inhibiting the release of glutamate [29,30] and increased glutamate reuptake [31,32].

Finally, epilepsy is a common comorbidity for RTT patients [33]. Riluzole is a long known anticonvulsant drug, which may be partly due to its inactivation of voltage-dependent sodium channels [34]. Animal study has demonstrated that riluzole treatment completely inhibited pre-ictal spikes and spike-wave discharges in the pilocarpine- and gamma-hydroxybutyrate lactone- induced epilepsy model [35]. These findings suggested that riluzole treatment can also reduce seizure in RTT subjects.

Evaluation of the hypothesis

The use of riluzole in RTT deserves a thorough examination, due in part to findings that have shown the glutamate levels tend to be increased and BDNF function is decreased in RTT. Several recommendations for applying this hypothesis of RTT treatment with riluzole are presented. Firstly, the availability of several mouse models of RTT based on MeCP2 dysfunction allowed testing of the potential therapeutic effect of riluzole in RTT subjects [36,37]. If there are promising results in animal studies, further double-blind, placebo-controlled randomized studies are required to confirm that riluzole had beneficial effects in patients with Rett syndrome. Second, recent study has established induced pluripotent stem cell (iPS cell) model of RTT [38]. RTT patient iPS cell-derived neurons showed changes in soma size, information encoding properties and synaptic connectivity that are defective in RTT [38]. The therapeutic potential of riluzole in RTT subjects could also be tested in this iPS model of RTT. Third, recent animal study found that riluzole (6–60 μg/ml) in tap water replacing regular drinking water for up to 3 weeks had dose-dependent antidepressant-like effects shown in the mouse forced swim test [39]. Another study found oral riluzole in drinking water (100 and 200 μg/ml) slowing the progression of neuromuscular dysfunction in the wobbler mouse [40]. The optimal dosage of riluzole for RTT treatment awaits further exploration. Fourth, it should be cautious that BDNF utilizes a dual receptor system to modulate diverse and sometimes opposing biological actions. Too much BDNF is harmful and has been implicated in the pathogenesis of epilepsy [41], anxiety [42] and even enhanced tumor cell survival [43]. Thus, there is an obvious need for studies assessing these potential harmful effects during riluzole treatment for Rett disease patients. Finally, both riluzole and antidepressant agents can increase brain BDNF levels. Use of the combination of both agents may provide the benefits for RTT subjects.

Conflict of interest statement

None.

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