Lithium and antidepressants: Potential agents for the treatment of Rett syndrome

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Summary

Rett syndrome (RTT) is a severe neurodevelopmental disorder occurring almost exclusively in females. It is caused by mutations in gene encoding methyl-CpG-binding protein 2 (MECP2) in the majority of cases. MECP2 was originally thought to be a global transcriptional repressor, but recent evidence from studies of animals suggests that it may have a role in regulating neuronal activity-dependent expression of specific genes such as Bdnf. A recent report demonstrated that deletion of Bdnf in MeCP2 mutants caused earlier onset/accelerated disease progression, whereas BDNF overexpression in the MeCP2 mutant brain led to later onset/slower disease progression, suggesting that manipulation of BDNF expression/signaling in the brain could be therapeutic for this disease. Lithium and antidepressants have been demonstrated to increase central BDNF levels or signaling in human as well as animal studies. Thus, it is proposed that these agents could have therapeutic potential for RTT subjects. Several points regarding the use of these agents in RTT are discussed. Further evaluation of the therapeutic effects of these drugs in RTT animal models is needed before clinical trials can begin.

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In 1999, mutations in the gene encoding methyl-CpG-binding protein 2 (MECP2) were identified as the primary cause of RTT [7], and MeCP2 mutations may account for close to 80% of RTT cases [8]. MECP2 is a methylated DNA-binding protein, which specifically binds to methylated DNA in vitro and represses transcription from methylated promoters [9,10]. In addition, recent study has also demonstrated that MECP2 may be implicated in regulating RNA splicing [11].

Brain-derived neurotrophic factor (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 systems in the central and peripheral nervous systems [12,13]. Like other neurotrophins, 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 (Trk), and a common low affinity receptor, p75 neurotrophin receptor [14,15]. Once BDNF is bound to the high affinity receptor TrkB, the receptor dimerises, auto-phosphorylates and initiates multiple signal transduction pathways that are involved in neurite outgrowth, morphological plasticity and the synthesis of proteins for differentiated function of neurons and synapses [for review see Ref. [16]]. In 2003, Bdnf was identified as a possible neuronal target gene for MECP2; in cultured neonatal cortical neurons, basal BDNF transcription is repressed in MeCP2-deficient neurons in the absence of neuronal activity, but activity-dependent upregulation of BDNF is unaffected in MeCpt2-deficient neurons [17]. From this finding, it seems that a MeCP2 mutant brain should express more BDNF than the wild-type brain. However, a recent report by the same study group showed that BDNF protein levels in the whole-brain lysate in MeCP2 knockout (KO) mice are decreased to about 70% of the wild-type level [18]. The apparently conflicting findings of the two reports could possibly be due to the differences in study design [18]. The earlier study was performed in vitro (neuronal cultures) and tested Bdnf RNA levels [17], while the later study compared BDNF protein levels in wild (normal neuronal activity) and MeCP2 KO brains [18]. It was hypothesized that MeCP2 deficiency decreases neuronal activity, thereby indirectly causing a decrease in BDNF protein level [18]. In this recent report, it was elegantly demonstrated that deletion of Bdnf in MeCP2 mutants caused an earlier onset/accelerated disease progression, whereas BDNF overexpression in the MeCP2 mutant brain led to a later onset/slower disease progression [18]. From these findings, the authors suggested that RTT pathogenesis may be partially mediated through BDNF, and therefore manipulation of BDNF expression/signaling in brain could be therapeutic for this disease [18].

Based on the findings detailed above and the conclusion, I propose that lithium and antidepressants, which could increase central BDNF levels, might be potential agents for the treatment of RTT. Animal studies have shown that chronic treatment with major classes of antidepressants [19–21] or lithium [22,23] has been found to increase the central BDNF protein levels and may restore hippocampal neurogenesis [19]. In humans, post-mortem study using immunohistochemistry has demonstrated that BDNF expression was increased in the hippocampus of depressed subjects treated with antidepressant medication at the time of death, compared with untreated analogs [24]. In addition, it has been found that BDNF serum concentrations are lower in untreated depressed subjects than healthy controls, and that antidepressant treatment in these patients can bring serum BDNF levels back to within the normal range [25]. Since animal studies have demonstrated that BDNF overexpression in the MeCP2 mutant brain leads to a later onset/slower disease progression [18], lithium or antidepressants, which could increase central BDNF levels, could have therapeutic potential for RTT. For the potential use of antidepressants or lithium in the treatment of RTT, several points are suggested:

First, the potential therapeutic effect of these agents in RTT subjects needs to be first evaluated in RTT animal models such as MeCP2 KO mice [17]. Second, for RTT subjects with cardiac conduction defects (e.g. prolonged QT intervals or epilepsy), certain antidepressant medications such as tricyclic antidepressants that may cause or aggravate these conditions should be avoided.

Third, the etiology of RTT is heterogeneous and MeCP2 mutations account for about 80% of RTT cases [8]. Whether increased BDNF-signaling has a therapeutic effect on RTT subjects without MeCP2 mutations may need further exploration.

Fourth, common genetic polymorphisms associated with BDNF expression may be related to the manifestations of or the BDNF-increasing agent therapeutic effects in RTT. There has been a report of a polymorphism (G196A) in the coding region of the Bdnf gene, which results in an amino acid change (Val66Met) [26]. This substitution has been shown to affect intracellular trafficking and activity-dependent secretion of BDNF and the Val/Val carriers have higher BDNF levels than Met allele carriers [26]. If increased BDNF expression is associated with later onset/slower disease progression...
in RTT animal models [18], it is likely that Val/Val carriers of RTT subjects will have better prognosis compared with Met allele carrier analogs, as Val/Val carriers have higher BDNF levels than Met allele carriers. This Bdnf Val66Met polymorphism has been associated with prophyllactic lithium response in bipolar disorder patients [27], thus its association with antidepressant or lithium treatment in RTT subjects may be worthy of further exploration.

Fifth, increasing central BDNF levels may improve part but not all RTT symptoms. For example, in the animal study, it was found that BDNF overexpression extended the lifespan, rescued a locomotor defect, and reversed an electrophysiological deficit observed in Mecp2 mutants [18]. BDNF-signalization has also been implicated in breathing control [for review see Ref. [28]]. Thus, lithium or antidepressants may be useful in treating respiratory dysfunction associated with RTT.

Finally, other strategies or agents that may increase central BDNF levels may be evaluated for potential use in treatment of RTT. For example, deltamethrin (DTM) is a widely used pyrethroid insecticide with a low acute toxicity in mammals. In a recent report, Imamura et al. demonstrated that administration of DTM to rat cortical neuronal cells in culture markedly increased Bdnf mRNA expression and the synthesis of protein at very low concentrations (10 nM−1 μM) [29]. The study also demonstrated that intraperitoneal administration of DTM (25 mg/kg) to rats increased the level of BDNF protein in the cerebral cortex and hippocampus [29]. Further, an earlier study demonstrated that administration of DTM (7 mg/kg orally for 15 days) markedly increased the wet weight of rat hippocampus [30]. Since DTM is a potent inducer of BDNF expression in neurons and BDNF-signalizing activation, it has been suggested as a potential antidepressant agent [31]. Whether DTM has a therapeutic effect in RTT could be evaluated in RTT animal models.

References


