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Peripheral administration of brain-derived neurotrophic factor to Rett syndrome animal model: A possible approach for the treatment of Rett syndrome

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Summary

Rett syndrome (RTT) is a postnatal, severe, disabling neurodevelopmental disorder occurring almost exclusively in females and is the second most common cause for genetic mental retardation in girls. In the majority of cases it is caused by mutations in gene (*MECP2*) encoding methyl-CpG-binding protein 2. Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor playing a major role in neuronal survival, neurogenesis and plasticity. Animal studies suggested that abnormalities in BDNF homeostasis may contribute to the pathogenesis in *Mecp2* null mice, and BDNF administration in the *Mecp2* mutant brain led to later onset/slower disease progression, suggesting that increased BDNF in the brain could be therapeutic for this disease. Mature BDNF is a 14 kDa protein that may have poor blood-brain barrier penetrability. However, recent animal studies demonstrated that peripheral administration of BDNF, either by intravenous injection or intranasal delivery, could increase BDNF levels in the brain. Thus it is proposed that peripheral administration of BDNF in the early stage could have therapeutic potential for RTT subjects. Furthermore, the combination use of mannitol may temporarily open the blood-brain barrier and facilitate the entry of BDNF into brain. The potential therapeutic effect of peripheral BDNF administration could be tested in RTT animal models such as *Mecp2* KO mice, which may provide a new intervention for this devastating disease.

key words: brain-derived neurotrophic factor • peripheral administration • blood-brain barrier • treatment • Rett syndrome

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BACKGROUND

Rett syndrome (RTT; OMIN # 312750) is a complex neurodevelopmental disorder characterized by the progressive loss of intellectual functioning and acquired speech, head growth deceleration, autistic features such as emotional withdrawal and diminished eye contact, motor stereotypies, early hypotonia followed by rigidity, epileptiform seizures, exaggerated responses to stress, and severe respiratory and autonomic (cardiac and gastrointestinal) dysfunction [1–3]. RTT predominantly affects girls and, in most cases, it is consequent to loss-of-function mutations in the gene (*MeCP2*) encoding methyl-CpG-binding protein 2 [4]. The basic pathophysiology of RTT is considered as deficiency of the activities of the serotonin (5-HT) and the noradrenaline (NA) neurons, which have roles in neuronal development in infancy from 4 months to 18 months of age [5,6]. Hypofunction of the 5-HT and NA neurons, which modulate the antigravity activities or postural tone, causes postural hypotonia and failure in locomotion (crawling) in infancy [7]. In addition to monoaminergic dysfunction, a study using receptor autoradiography demonstrated that Rett syndrome is a genetic disorder of synapse development, especially synapses that use glutamate and GABA as neurotransmitters [8]. To date, no successful medical treatments have been established; current treatment includes symptomatic therapy, anticonvulsive therapy and physiotherapy.

Brain-derived neurotrophic factor (BDNF) belongs to a family of proteins related to the nerve growth-factor family, widely expressed in the adult mammalian brain and responsible for neuron proliferation, survival and differentiation [9,10]. BDNF is also found in the blood, accumulating predominantly in platelets; a rodent study showed that serum and cortical BDNF levels undergo similar changes during maturation [11]. 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) and a common low-affinity receptor (p75 neurotrophin receptor) [12,13].

In 2006, Chang et al. demonstrated that BDNF levels in the whole-brain lysate in *Mecp2* knockout (KO) mice are decreased to about 70% of the wild-type levels [10]. It was hypothesized that *Mecp2* deficiency decreases neuronal activity, thereby indirectly causing a decrease in BDNF protein levels [14]. In their report, it was also 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, suggesting that RTT pathogenesis may be partially mediated through BDNF; therefore, manipulation of BDNF expression/signaling in brain could be therapeutic for this disease [14]. This notion is supported by the recent report that synaptic dysfunction in the brainstem nucleus tractus solitarius (the principal site for integration of primary visceral afferent inputs to central autonomic pathways) of *Mecp2* mutants could be rescued by application of exogenous BDNF [15]. In another study, *Bdnf* overexpression in embryonic day-18 hippocampal neurons prevents dendritic atrophy caused by *Mecp2* mutations [16]. In a clinical study, it was found that a *BDNF* functional genetic polymorphism may affect Rett severity [17].

On the basis of the above findings, agents such as lithium, antidepressants [18], and glatiramer acetate [19] that could increase central BDNF levels may have potential for the treatment of RTT. In animal studies it was demonstrated that desipramine, a tricyclic antidepressant, can improve breathing and survival in a RTT mouse model [20,21]. Recently, it has been suggested that early intervention with antidepressants or psychostimulants could increase the *MeCP2* expression in females with RTT and normalize BDNF deficiency to improved Rett syndrome [22].

For a more direct intervention, here I propose that peripheral BDNF administration, either by intranasal delivery or intravenous injection, could be a possible approach for the treatment of Rett syndrome.

HYPOTHESIS

Like other secreted proteins, BDNF arises as a precursor, pro-BDNF, which is proteolytically cleaved to yield the mature protein. Mature BDNF is a 14 kDa protein that may have poor blood-brain barrier penetrability. However, earlier animal studies demonstrated that peripheral BDNF by intravenous injection can cross the blood-brain barrier [23–25]. In a recent report, Schmidt et al demonstrated that peripherally administered BDNF (by a subcutaneously implanted osmotic mini-pump) produces antidepressant-like cellular responses in the mouse brain as well as antidepressant-like behaviors [26]. In addition, hippocampal neurogenesis was increased and BDNF levels were elevated in the hippocampus of adult mice after chronic, peripheral BDNF administration [26]. These findings suggest that peripheral BDNF has behavioral and cellular effects that are similar to antidepressants [26]. Regarding intranasal delivery of BDNF, a recent animal study by Alcalá-Barraza et al demonstrated that intranasal delivery of [(125)I]-radiolabeled BDNF resulted in increased BDNF concentrations within 25 min in brain parenchyma [27]. In addition, not only did BDNF reach the brain, it also activates the pro-survival PI3Kinase/Akt pathway [27].

EVALUATION AND DISCUSSION

For the potential use of peripheral BDNF administration in the treatment of RTT, several points are suggested:

First, the potential therapeutic effect of peripheral BDNF administration in RTT subjects could be evaluated in RTT animal models such as *Mecp2* KO mice, which may provide a new strategy for the treatment of this devastating disease. It should be noted that *Mecp2* KO mice are a useful model to understand the physiological role of the protein in Rett disease, but usually Rett patients are not fully deleted but have a truncated *Mecp2* protein, thus data from peripheral administration of BDNF in *Mecp2* KO mice would certainly not be exhaustive.

Second, although BDNF plays important roles in neuronal development, function and survival, it should be cautioned that too much BDNF is harmful and has been implicated in the pathogenesis of epilepsy [28], mania [29], anxiety [30] and enhanced tumor cell survival [31]. Thus, there is an obvious need for studies assessing the optimal dose of BDNF for Rett disease patients.

Third, mannitol, an osmotic diuretic agent, can be used to open the blood-brain barrier by temporarily shrinking the tightly coupled endothelial cells that make up the barrier. A recent study in rats demonstrated that it can facilitate the entry of neurotrophic factors, such as BDNF, from the periphery into the adult stroke brain [32]; thus, combination use of mannitol may increase brain BDNF levels and improve the therapeutic effect of intravenous injection of BDNF in the treatment of Rett syndrome. However, it should be cautioned that mannitol may induce some adverse effects, including severe allergic reactions, blurred vision, chest pain, chills or fever, confusion, headache, muscle cramps, and weakness [33].

Fourth, the basic pathophysiology of RTT is considered as deficiency of the activities of the 5-HT and the NA neurons, which have roles in neuronal development in infancy from 4 months to 18 months of age [1,5,7]. Sleep studies in children with RTT also suggested that the behavior in early infancy is due to the hypofunction of these monoaminergic systems in the brain stem [1,5]. These cause poor response to environmental stimulation, poor formation of circadian rhythm, and more sleeping during daytime, which also induces autistic tendency. The axons of the 5-HT neurons involving the development of the central neurons system are pruned early, probably by absence of MeCP2. Restriction of atonia in rapid eye movement (REM) stage from the fourth month of age induces synaptogenesis of the brain and enables integrative function of the brain [1,5]. BDNF plays key roles in neuronal development and differentiation (ie, promoting dendritogenesis and synaptogenesis) [10]. This suggests early intervention with BDNF may improve the hypofunction of these monoaminergic systems in Rett patients.

Finally, RTT is a neurodevelopment disorder and BDNF plays a critical role in neuron proliferation and differentiation. Testing BDNF administration in animal models at different ages and with different durations could be informative. An early intervention with BDNF may be required to decrease the detrimental consequences of this disorder.

CONCLUSIONS

Increased BDNF in the brain could be therapeutic for RTT disease. Animal studies demonstrated that peripheral administration of BDNF, either by intravenous injection or intranasal delivery, could increase BDNF levels in the brain. The hypothesis of peripheral treatment with BDNF in Rett patients is rather far from clinical application. Before that can occur, many studies must be conducted in more than one animal model. Potential adverse effects of a peripheral treatment with a growth factor should also be seriously considered, as well as the feasibility (and economic burden) of BDNF treatment.

Conflicts of interests

There are no conflicts of interests to report.

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