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The role of BDNF in the mechanisms of autistic-like behavior in BTBR mice

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Motivation and Aim: The mechanisms underlying autism spectrum disorder (ASD) are still poorly understood, but impaired neuroplasticity undoubtedly plays an important role in the development of the disease. Brain-derived neurotrophic factor (BDNF) significantly implicated in regulation of neuronal plasticity and behavior. In addition, a large number of human and animal studies indicate the involvement of BDNF in the pathogenesis of ASD [1, 2]. The reduced BDNF mRNA and protein levels in the hippocampus and the frontal cortex of BTBR mice (validated as the model for ASD) have been demonstrated in a few studies [3, 4] but these data are scarce and incomplete.
Methods and Algorithms: Here we investigated *Bdnf* exon transcripts expression as well as BDNF and its precursor proBDNF proteins in the hippocampus (HC), frontal cortex (FC), striatum (ST) and midbrain (MB) of BTBR mice in comparison with normosocial C57Bl/6 mice. Compensation of the deficits of mature BDNF in BTBR mice was performed by either i.c.v. injection of recombinant BDNF protein or its overexpression in neurons using AAV vectors encoding *Bdnf* gene under synapsin promoter.
Results: It was found that mRNA levels of *Bdnf* exons 1–4 were decreased in HC of BTBR mice. In the ST of BTBR mice the number of transcripts *Bdnf* exons 1, 2, 4 was also decreased. The mRNA levels of *Bdnf* exons 1 and 6 were decreased in FC of BTBR mice. The proBDNF level as well as proBDNF/BDNF ratio were increased in HC and ST of BTBR mice.
Administration of BDNF protein failed to affect the behavior of BTBR mice. However, a decrease in the proBDNF/BDNF ratio in ST was detected after i.c.v injection of BDNF. Hippocampal overexpression of BDNF significantly reduced anxiety-related and stereotyped behavior of BTBR mice without affecting their social interest. In contrast, overexpression of BDNF in the FC of BTBR mice exclusively increased social interest but not other types of behaviors.
Conclusion: Thus, we have shown for the first time the significant changes in expression of specific *Bdnf* transcripts that may underlie impaired BDNF maturation in BTBR mice as evidenced by the proBDNF prevalence. Also, it was demonstrated that direct compensation of mature BDNF deficit by induction of BDNF overexpression can ameliorate autistic-like behavior in BTBR mice, but this effect is strongly dependent on the target brain structure.
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