



REVIEW

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Abnormalities in the zinc-metalloprotease-BDNF axis may contribute to megalencephaly and cortical hyperconnectivity in young autism spectrum disorder patients

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Abstract

Whereas aberrant brain connectivity is likely the core pathology of autism-spectrum disorder (ASD), studies do not agree as to whether hypo- or hyper-connectivity is the main underlying problem. Recent functional imaging studies have shown that, in most young ASD patients, cerebral cortical regions appear hyperconnected, and cortical thickness/brain size is increased. Collectively, these findings indicate that developing ASD brains may exist in an altered neurotrophic milieu. Consistently, some ASD patients, as well as some animal models of ASD, show increased levels of brain-derived neurotrophic factor (BDNF). However, how BDNF is upregulated in ASD is unknown. To address this question, we propose the novel hypothesis that a putative zinc-metalloprotease-BDNF (ZMB) axis in the forebrain plays a pivotal role in the development of hyperconnectivity and megalencephaly in ASD.

We have previously demonstrated that extracellular zinc at micromolar concentrations can rapidly increase BDNF levels and phosphorylate the receptor tyrosine kinase TrkB via the activation of metalloproteases. The role of metalloproteases in ASD is still uncertain, but in fragile X syndrome, a monogenic disease with an autistic phenotype, the levels of MMP are increased. Early exposure to lipopolysaccharides (LPS) and other MMP activators such as organic mercurials also have been implicated in ASD pathogenesis. The resultant increases in BDNF levels at synapses, especially those involved in the zinc-containing, associative glutamatergic system may produce abnormal brain circuit development. Various genetic mutations that lead to ASD are also known to affect BDNF signaling: some down-regulate, and others up-regulate it. We hypothesize that, although both up- and down-regulation of BDNF may induce autism symptoms, only BDNF up-regulation is associated with the hyperconnectivity and large brain size observed in most young idiopathic ASD patients.

To test this hypothesis, we propose to examine the ZMB axis in animal models of ASD. Synaptic zinc can be examined by fluorescence zinc staining. MMP activation can be measured by in situ zymography and Western blot analysis. Finally, regional levels of BDNF can be measured. Validating this hypothesis may shed light on the central pathogenic mechanism of ASD and aid in the identification of useful biomarkers and the development of preventive/therapeutic strategies.

Keywords: Autism spectrum disorder (ASD), Zinc, Metalloprotease, Brain-derived neurotrophic factor (BDNF)

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