Positive effect of exogenous brain-derived neurotrophic factor on impaired neurite development and mitochondrial function in dopaminergic neurons derived from dental pulp stem cells from children with attention deficit hyperactivity disorder

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論　文　名	Positive effect of exogenous brain-derived neurotrophic factor on impaired neurite development and mitochondrial function in dopaminergic neurons derived from dental pulp stem cells from children with attention deficit hyperactivity disorder （患者由来歯髄幹細胞を活用した注意欠如・多動症の病態研究）
論文調査委員	主　査　　九州大学　　教授　　清島　保 副　査　　九州大学　　教授　　自見　英治郎 副　査　　九州大学　　教授　　久木田　敏夫

論　文　審　査　の　結　果　の　要　旨

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders and is characterized by impaired attention, hyperactivity, and impulsivity. While multiple etiologies are implicated in ADHD, its underlying mechanism(s) remain unclear. Although previous studies have suggested dysregulation of dopaminergic signals, mitochondria, and brain-derived neurotrophic factor (BDNF) in ADHD, few studies have reported these associations directly. Stem cells from human exfoliated deciduous teeth (SHED) can efficiently differentiate into dopaminergic neurons (DNs) and are thus a useful disease-specific cellular model for the study of neurodevelopmental disorders associated with DN dysfunction. This study aimed to elucidate the relationships between DNs, mitochondria, and BDNF in ADHD by analyzing DNs differentiated from SHED obtained from three boys with ADHD and comparing them to those from three typically developing boys. In the absence of exogenous BDNF in the cell culture media, DNs derived from boys with ADHD (ADHD-DNs) exhibited impaired neurite outgrowth and branching, decreased mitochondrial mass in neurites, and abnormal intracellular ATP levels. In addition, BDNF mRNA was significantly decreased in ADHD-DNs. Supplementation with BDNF, however, significantly improved neurite development and mitochondrial function in ADHD-DNs. These results suggest that ADHD-DNs may have impaired neurite development and mitochondrial function associated with insufficient production of BDNF, which may be improved by exogenous BDNF supplementation.

These observations suggest that the patient-derived SHED may contribute to the future development of treatment strategies for aberrant dopaminergic signaling, mitochondrial functioning, and BDNF levels implicated in ADHD pathogenesis. Based on this research, the candidate deserves to be conferred the degree of DOCTOR OF PHILOSOPHY (Dental Science) in the Graduate School of Dentistry, Kyushu University.