Insulin-like growth factor binding protein (IGFBP)-3 regulates IGF bioactivity, induces apoptosis, and inhibits cell growth independent of IGFs, but the functional role of IGFBP3 in the brain is not clear. In the present study, we revealed the effect of IGFBP3 on the brain by characterizing the phenotype of Igfbp3-null mice. Compared with wild-type mice, Igfbp3-null mice had significantly decreased IGF-1 content in the brain but no change in weights of brain and body. In Igfbp3-null mice, the number of dendritic spines was significantly reduced, and the dendritic diameter was thickening. In addition, in Igfbp3-null mice, a decrease in phosphorylated Akt and ERK1/2 significantly reduced PSD-95 expression, and GAD65/67 expression was significantly decreased. These results indicate that IGFBP3 deficiency impairs neuronal structure and signaling. In behavioral studies, Igfbp3-null mice were hyperactive, and a Y-maze alternation test revealed impaired spatial working memory but no anxiety-like behavior. Monoaminergic analysis using high-performance liquid chromatography indicated that Igfbp3-null mice had lower levels of dopamine and serotonin compared with wild-type mice, suggesting an abnormal monoaminergic neurotransmission. In conclusion, our studies found that the deletion of IGFBP3 results in behavioral impairments that are associated with abnormal synaptic function and monoaminergic neurotransmission, which helps to characterize the critical role of IGFBP3 in the brain.

deficiency in the developing brain impairs neurogenesis, synaptogenesis, and myelination, resulting in neuronal death. IGFBP3 specifically regulates the IGF-1-mediated neural progenitor cell proliferation via down-regulation of phosphorylated Akt and cyclin D1. The Igfbp3 transgenic mouse has a decreased brain weight and a reduction in neural proliferation in the periventricular zone, indicating a potential role for IGFBP3 in brain growth and neurogenesis.

Moreover, IGFBP3 is downstream of MECP2. MECP2, the causative gene of the neurodevelopmental disorder Rett syndrome, directly binds to the promoter of IGFBP3 and regulates its expression. MECP2 deficiency in patients and mice with Rett syndrome causes an increased expression of IGFBP3. On the other hand, MECP2 duplication syndrome and Mecp2-overexpressed mice have the similar phenotypes of Rett syndrome, such as mental retardation and autistic behavior. We can speculate IGFBP3 dose-dependent psychomotor phenotypes, although the IGFBP3 effect caused by excess MECP2 is not yet known. IGFBP3 functional characterization in the brain may be of benefit to understand the pathogenesis of some neurologic diseases, such as MECP2-related disorders. In the present study, we clarified the effect of IGFBP3 on the brain by investigating the phenotypic character of Igfbp3-null mice.

Materials and Methods
Preparation of Igfbp3-Null Mice
Cryopreserved mouse sperm with the Igfbp3<sup>tm1(KOMP)Vlcg</sup> allele of the C57BL/6N strain completely replaced with

![Figure 1](image-url)
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