学位論文抄録

Study of draxin and Tsukushi function in brain development and injury

（脳発生と障害における draxin と Tsukushi の果たす機能解析）

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Abstract of the Thesis

Background and Purpose: Previously we reported the identification of two secreted proteins: draxin and Tsukushi (TSK). *Draxin* knockout mice showed agenesis of all forebrain commissures: corpus callosum (CC), hippocampal commissure (HC), and anterior commissure (AC). Moreover, genetic deletion of *TSK* in mice also results in the agenesis of AC and CC, also suggesting the importance of TSK function in forebrain commissure formation. As both *draxin* and *TSK* single mutant mice converge into common phenotypes, there is a possibility that the combined function of these two proteins is essential for the formation of forebrain commissures. Furthermore, we documented that draxin exerts its chemorepulsive function through netrin's chemoattractive receptor, DCC. As different ligands interacted with the same receptor, DCC and shows opposite functions of axon guidance, there might be some other molecule(s) that also interact with DCC to perform the opposite signaling pathway. Additionally, we also tried to explore the function of draxin after brain injury.

Methods: To analyze the forebrain commissures, we generated *draxin/TSK* doubly homozygous and heterozygous mice; and histological, biochemical and in vitro culture was performed. Antibody production, co-immunoprecipitation and mass spectrometry analysis were performed to identify the receptor-associated molecule(s) by proteomics approach. To explore the new function of draxin global cerebral ischemia and middle cerebral artery occlusion were performed in adult mice.

Results: Higher prevalence of CC malformation and agenesis of the AC in the *draxin/TSK* doubly homozygous and heterozygous mice implies the genetic interaction between draxin and TSK. Importantly, in this study, we established TSK as a new chemorepulsive axon guidance molecule that function to guide anterior olfactory neuronal (AON) and cortical axons. We also observed that TSK and draxin had additive effects in inhibiting cortical and AON neurite outgrowth. Besides, we found some probable candidates as the DCC receptor associated molecules. Furthermore, we found that draxin is re-expressed and/or up regulated in the dentate gyrus and olfactory bulb after ischemia.

Conclusion: Combined guidance activities of draxin and TSK regulate forebrain commissure formation. DCC might have some partner molecules to exert its opposite signal transduction and there is a high possibility that draxin has some new roles along with axon guidance.