学位論文抄録

Inhibitory effects of draxin on axonal outgrowth and migration of precerebellar neurons

（前小脳神経細胞の移動と軸索伸長に対する draxin の阻害効果）

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Abstract

Background and Purpose: During the formation of intricate neural circuits, axons respond to a variety of guidance cues, attractive guidance cues induce axonal turning towards them, while repulsive guidance cues repel axons away or cause axon retraction. Some molecules show both attractive and repulsive guidance activity depending on concentration, receptor distribution, and distribution of other guidance cues. Our group previously identified an axon guidance molecule named draxin, which is essential for formation of spinal cord and forebrain commissure. *Draxin* expressed in various part of nervous system. In this study we analyzed draxin function in precerebellar neurons (PCN) migration in hindbrain and in thalamocortical axon projections in forebrain.

Methods: In situ hybridization, β-gal staining and draxin immunostaining were performed to check draxin expression pattern at different developmental stages. Immunostaining against several markers and DiI labeling were used to check the axonal projection and neuronal distribution between wild type and *draxin*$^{-/-}$ littermate mice. To conclude draxin function in vitro we performed explant culture and dissociated neuron culture.

Results: We found draxin strongly expressed in the rhombic lip from where PCN start to migrate towards the floor plate. Draxin inhibited axonal outgrowth and neuronal migration from the rhombic lip explants. However PCN migration was unaltered in *draxin*$^{-/-}$ mice. We also analyzed role of draxin in thalamocortical axon projection. We observed severe defect in thalamocortical axon projection in *draxin*$^{-/-}$ mice, the phenotype observed in *draxin*$^{-/-}$ mice can be rescued by draxin expression in neocortex. Interestingly draxin promoted thalamic neurite outgrowth at lower concentration. We established several culture conditions, which mimic physiological concentration of draxin, in such case we observed neurite growth promotion. We also identify DCC and Neogenin as functional receptor for draxin's function in thalamocortical axon projection.

Conclusion: Our results indicate draxin and other guidance cues may have redundant role in PCN migration. In thalamocortical axon projection, draxin expression in the neocortex is essential for thalamocortical axon projection. Our findings further indicate DCC and Neogenin as functional receptor for draxin in thalamocortical axon projection.