学位論文抄録

Draxin inhibits olfactory bulb and cortical axonal outgrowth through the netrin receptor DCC

（ドラキシンは嗅球と大脳皮質からの軸索成長を
ネトリン受容体であるDCCを介して阻害する）

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Abstract of the Thesis

Background: We recently reported a novel class of axon guidance molecule, draxin. *Draxin* is expressed in different regions of mammalian brain. In vitro, draxin can repel spinal commissural axons whose outgrowth is stimulated by netrin-1; *in vivo*, genetic deletion of *draxin* results in mild guidance defects of those axons, and in a dramatic loss of all forebrain commissures (**Science** 323: 388-393, 2009).

Purpose: Since *draxin* is strongly expressed in the neocortex of mammalian brain, the first purpose of this study to assess the draxin function in the development of lateral olfactory tract (LOT), an axonal tract that transfer the olfactory sensory information from the olfactory bulb to the olfactory cortex. Draxin is a secreted axon guidance molecule and its function must be mediated by receptor. Therefore, the second purpose of this study is to identify the receptor/s for draxin.

Methods: Draxin mRNA and protein expression in different developmental stages were checked by LacZ staining and immunohistochemistry. Its in vitro and in vivo functional analysis for olfactory bulb axons were carried out by explant culture assay and checking the LOT phenotype in *draxin-/-* mouse. To identify the functional receptor for draxin, several candidate receptors were screened for draxin binding. After finding the promising candidate, the ligand binding was confirmed by biochemical and immunohistochemical analysis. Finally, for the functional analysis, draxin`s axonal outgrowth inhibitory role was checked on the receptor knockout neurites.

Results: Draxin inhibits olfactory bulb axonal outgrowth in vitro. Overall, the LOT in *draxin-/-* mice was normal despite mild defasciculation within the tract of these mutants. Draxin binds specifically and with subnanomolar affinity to the netrin receptor DCC, in a region of DCC distinct from its netrin-binding domain. *In vitro*, neurites from cortical and olfactory bulb explants of *DCC-/-* mice show a dramatic reduction in binding of draxin, and their outgrowth is significantly less inhibited by draxin, when compared with neurites from explants of wild type mice.

Conclusion: These results demonstrate that draxin is involved in the LOT development and its axonal outgrowth inhibitory function is mediated by the netrin receptor DCC.