Title	The role of UNC5H4 in cortical development
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論　文　内　容　の　要　旨

During development, neurons differentiate into specific cell types with distinct cell morphology, physiological properties and neural connections. One major question in developmental neuroscience is how cell type-specific differentiation is regulated. In general, it is known that intrinsic and extrinsic factors cooperate to regulate cell specification and differentiation. In the neocortex, neurons display different characteristics according to their laminar and area locations. Although much progress has been made in understanding the molecular basis for intrinsic regulations of laminar and area specification, it is still poorly understood how lamina- and area-specific molecules such as membrane-associated proteins contribute to cortical development through interacting with extrinsic cues.

In this thesis, I studied the molecular mechanisms underlying layer-specific cortical development, focusing on layer 4. For this purpose, I searched for the genes that are expressed in layer 4 of the developing rodent neocortex by constructing a subtraction cDNA library. As a result, unc5h4, a netrin receptor family member, was identified. In situ hybridization analysis revealed that unc5h4 gene was expressed strongly in layer 4 of the primary sensory cortices, the target of sensory thalamic afferents.

To determine the ligand of UNC5H4, protein binding to UNC5H4 was examined. The result showed that netrin-4 as well as netrin-1 protein bound to UNC5H4-expressing HEK293T cells. Expression of netrin-4 gene was observed in the neocortex with a higher level in layer 4 and sensory thalamic nuclei, suggesting that netrin-4 can affect cortical neurons which express unc5h4. To further study the role of UNC5H4 in cortical development, the effect of netrin-4 on unc5h4-expressing cortical neurons was investigated using dissociated cell culture. I found that cell death of unc5h4-expressing layer 4 cells was suppressed by the application of netrin-4 protein. In contrast, netrin-4 had no effect on deep layer cells even though unc5h4 was overexpressed. These results suggest that UNC5H4 is predominantly expressed in layer 4

neurons in the primary sensory areas of the developing neocortex and may mediate the effect of netrin-4 on cortical cell survival in a lamina-specific manner.

論　文　審　査　の　結　果　の　要　旨

　申請者は、大脳皮質の層特異的な細胞分化に興味を持ち、発生期大脳皮質の第４層に特異的に発現する分子の探索を行い、unc5h4遺伝子が発達期げっ歯類一次感覚野の第4層に強く発現することを見出した。次に、UNC5H4が大脳皮質細胞の発達に果たす役割を明らかにすることを目的として、リガンド分子の検索を行い、さらに分散培養系を用いて機能解析を行った。その結果、netrin-4タンパク質がUNC5H4発現細胞に結合する可能性、およびnetrin-4の遺伝子が大脳皮質上層および視床に発現することが示された。さらに、分散培養下の皮質第4層細胞において、UNC5H4がnetrin-4による細胞生存効果を媒介したが、深層細胞では機能しないことを示唆した。以上の結果から、UNC5H4はnetrin-4との相互作用により層特異的な細胞の生存を調節することが示唆された。

　以上のように、本論文は脳の細胞分化の解明において有用な知見であると考えられ、博士（理学）の学位論文として価値があるものと認める。