論文の内容の要旨

論文題目　Elucidation of Molecular Mechanisms Underlying Ca^{2+}/Calmodulin-Dependent Protein Kinase Iγ Activation during Dendritogenesis of Developing Cortical Neurons

（発達期大脳皮質神経細胞の樹状突起形成におけるカルシウム/カルモデュリン依存性蛋白リン酸化酵素 Iγ活性化の分子機構の解明）

鈴木　敢三

Ca^{2+} is a pleiotropic second messenger that plays a key role in regulation of neuronal morphogenesis. Ca^{2+}/calmodulin-dependent protein kinases (CaMKs) are good candidates as potential downstream effectors of Ca^{2+} elevation in neurons. We previously found that distinct limbs of the CaMKK-CaMKI cascade were specifically implicated in determining the extent of either dendritic or axonal growth downstream of different growth guidance signals in cultured cortical neurons. A membrane-anchored CaMKIγ regulated dendritogenesis downstream of BDNF, while in contrast, cytosolic CaMKIα strongly promoted axonal outgrowth and arborization downstream of excitatory GABA. However the key molecular mechanisms controlling the dendritogenetic and axonogenetic selectivity of CaMKIγ and CaMKIα have not been addressed. Here I demonstrate the activation mechanisms of the CaMKIγ downstream of BDNF in developing cortical neurons. I found that BDNF selectively stimulated CaMKIγ-dependent dendritic growth and enhanced the maximal

activity of CaMKIγ, but not CaMKIα. The present *in vitro* study revealed that CaMKIγ was a privileged sensor for small Ca^{2+} rises. Furthermore, distinctive substrate signatures were identified for CaMKIγ and CaMKIα based on peptide library profiling analysis. Thus, a lower Ca^{2+} threshold for activation of CaMKIγ, in combination with an altered substrate specificity and a dendritic enrichment through raft anchoring, may be key molecular mechanism of CaMKIγ-mediated selective dendritogenesis downstream BDNF during development of immature cortical neurons.