博 士 論 文 の 内 容 の 要 旨

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論文題目	Studies on roles of lysophosphatidylethanolamine in neuronal morphology and survival （神経細胞の形態と生存におけるリゾホスファチジルエタノールアミンの働きに関する研究）

（博士論文の内容の要旨）

The brain is one of the most lipid-rich organs, especially phospholipids play important roles not only in membrane organization but also in brain function. In this study, I aimed to identify and characterize the phospholipids that regulate biological processes of CNS neurons.

First, I applied 10 different phospholipids to cultured cortical neurons and found that lysophosphatidylethanolamine (LPE) stimulates neurite outgrowth. Structurally different LPE species, 16:0 LPE and 18:0 LPE, exerted same effect on the neurite outgrowth. Interestingly, 16:0 LPE-stimulated neurite outgrowth was inhibited by the inhibitor of Gq/11 protein. On the other hand, 18:0 LPE-stimulated neurite outgrowth was inhibited by the inhibitor of Gi/Go proteins. The effects of PKC inhibitors on neurite outgrowth were different between these LPEs. I also found that these LPEs activate MAPK to the same extent. However, the effects of MAPK inhibitor on neurite outgrowth were also different between these LPEs. These results suggest that the structurally different LPE species, 16:0 LPE and 18:0 LPE, stimulate neurite outgrowth through distinct G protein-coupled receptors and signaling pathways.

Next, I performed comprehensive quantitative LC-ESI-MS/MS analysis of LPE species and showed their composition in the brain. I found that 18:1 LPE, which is a major composition of the mouse brain LPE species, stimulates neurite outgrowth in cultured cortical neuron. Inhibitor experiments suggest that the effects of 18:1 LPE on neurite outgrowth is mediated by GPCR-activated Gq/11 protein and its downstream PLC/PKC/MAPK. Noteworthy, I found that 18:1 LPE protects cultured cortical neurons against glutamate-induced excitotoxicity, and involvement of PKC inhibitor Go6983-sensitive PKC in this protective effect of 18:1 LPE. These results suggest that 18:1 LPE, one of the abundant LPE species in the brain, exerts the stimulation of neurite outgrowth and protection against glutamate-induced excitotoxicity in cultured cortical neurons.

Conclusion: In these studies, I demonstrate the roles of LPE in CNS neurons. My findings establish the grounds for further investigation of the physiological and pathological roles of LPEs in the brain.