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様式１０２

学位論文の内容の要旨

Summary of the Substance of Dissertation

専　攻 Major Field	Medicine	部　門 Department	
学籍番号 Student No.	19D741	氏　名 Name	RAHMAN SM KHALEDUR
論文題目 Thesis Subject	**Formation of *N*-acyl-phosphatidylethanolamines by cytosolic phospholipase $A_2\varepsilon$ in an ex vivo murine model of brain ischemia**		

（論文要旨）

Summary

Background: *N*-Acyl-phosphatidylethanolamines (NAPEs) are a minor class of membrane glycerophospholipids and accumulate along with their bioactive metabolites, *N*-acylethanolamines (NAEs), during brain ischemia. NAPEs can be formed through *N*-acylation of phosphatidylethanolamine, which is catalyzed Ca^{2+}-dependently by cytosolic phospholipase $A_2\varepsilon$ ($cPLA_2\varepsilon$, also known as PLA2G4E) or Ca^{2+}-independently by members of the phospholipase A and acyltransferase (PLAAT) family. However, the enzyme responsible for the NAPE production in brain ischemia has not yet been clarified.

Purpose: The purpose of the present study was to evaluate the contribution of $cPLA_2\varepsilon$ to the NAPE formation in brain using $cPLA_2\varepsilon$ gene-disrupted ($Pla2g4e^{-/-}$) mice. In particular, I analyzed the accumulation of NAPEs and NAEs in a post-decapitative brain ischemic model.

Methods: The enzyme activity and expression levels of $cPLA_2\varepsilon$ were examined by the measurement of Ca^{2+}-dependent NAPE formation and quantitative PCR, respectively. Endogenous brain levels of NAPEs and NAEs were analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). In the post-decapitative brain ischemic model, decapitated mouse brains were incubated at 37　for 6 h.

Results and discussion: As analyzed with brain homogenates of wild-type mice, the age dependency of Ca^{2+}-dependent NAPE-forming enzyme activity showed a bell-shape pattern being the highest at the first week of postnatal life. The expression level of $cPLA_2\varepsilon$ mRNA was also higher in neonatal brain. In contrast, the enzyme activity was completely abolished in $Pla2g4e^{-/-}$ mice, showing that $cPLA_2\varepsilon$ is responsible for the Ca^{2+}-dependent NAPE formation in brain. However, LC-MS/MS analysis revealed that endogenous brain levels of NAPEs were similar between wild-type and $Pla2g4e^{-/-}$ mice, suggesting

the involvement of other enzyme(s). I next focused on the post-decapitative brain ischemic model. In the decapitated brain of wild-type mice, NAPEs and NAEs were remarkably accumulated, while these brain levels were only slightly increased in Pla2g4e$^{-/-}$ mice. These results suggested that cPLA$_2\varepsilon$ is principally responsible for the formation of NAPEs during brain ischemia. Since NAEs were reported to show anti-inflammatory and cytoprotective effects, the NAEs produced during ischemia may be beneficial to the improvement of symptom.

Conclusion: By using Pla2g4e$^{-/-}$ mice, I showed that cPLA$_2\varepsilon$ is principally responsible for the postmortem production of NAPEs and NAEs in the brain for the first time. However, other enzyme(s) appeared to be involved in the maintenance of basal NAPE levels in non-damaged brain tissues.

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(備考) 論文要旨は，日本語で１，５００字以内にまとめてください。
(Recital) Sum up the within １５００ letters.