論文の内容の要旨

Physiological functions of neurosteroids produced by steroid 7α-hydroxylase CYP7B1 in mice

(ステロイド 7α水酸化酵素 CYP7B1 により合成される マウスニューロステロイドの生理機能解析)

氏　名　　前畑　佳納子

Neuroactive steroids, termed neurosteroids, are synthesized *de novo* in the brain and influence biological functions including behavior and higher brain function. These neurosteroids are synthesized from cholesterol by a series of enzymes, among which one of the P450 hydroxylases, cytochrome P450-7b1 (CYP7B1), catalyzes formation of 7-hydroxylated neurosteroids, 7α-hydroxypregnenolone (7α-OH-Preg) and 7α-hydroxydehydroepiandrosterone (7α-OH-DHEA). In this study, I found higher levels and diurnal expression of *Cyp7b1* mRNA in the mouse hippocampus among various brain regions, and identified 7α-OH-Preg and 7α-OH-DHEA in the mouse hippocampal extract by using ultra-performance liquid chromatography coupled with electrospray-tandem mass spectrometry in negative ion mode. This is the first report to identify these steroids in the mouse brain without derivatization for mass spectrometry. Then, I investigated behavioral phenotype of *Cyp7b1*-deficient mice. Intriguingly, *Cyp7b1*-deficiency did not affect recent memory but impaired

remote memory in the Morris water maze test. Furthermore, chronic intracerebroventricular administration of a mixture of 7α-OH-Preg and 7α-OH-DHEA improved remote spatial memory performance of *Cyp7b1*-deficient mice. These results demonstrate that the 7α-hydroxylated neurosteroids regulate long-term maintenance of spatial memory in mice.