

論 文 内 容 要 旨

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| 学位論文題目 | Study on metabolism of very long-chain fatty acids in peroxisomes and their related disease (極長鎖脂肪酸のペルオキシソームにおける代謝と関連疾患に関する研究) | | |
| <p>内容要旨</p> <p>Very long-chain fatty acids (VLCFAs) are FAs with carbon chains more than C20. Metabolic breakdown of VLCFAs takes place exclusively in peroxisomes. It has been known that genetic mutations of enzymes involved in peroxisomal β-oxidation cause abnormal accumulations of VLCFAs, such as C24:0 FA and C26:0 FA, and that these mutations induce several neurological disorders in human called peroxisomal disease. However, the link between accumulations of the VLCFAs and neurological dysfunctions remains obscure. One of difficulties in the biological study of VLCFAs is their low solubility in aqueous medium. In this study, I found that adding isopropanol solution of VLCFAs into aqueous albumin at warmed condition helped the formation of VLCFA/albumin complex. Using this solubilizing technique, I examined uptake, metabolism and biological effect of extracellular VLCFAs in peroxisome-deficient Chinese hamster ovary (CHO) cells.</p> <p>Experiments with C22:0, C23:0, C24:0, C25:0, and C26:0 FA revealed that accumulations of these saturated VLCFAs in cellular lipids were suppressed to quite low level in both peroxisome-deficient and wild-type CHO cells. The suppression mechanisms operated in these types of cells are different, those are “non-uptake” and “peroxisome-dependent clearance” manner, respectively. In contrast, incubation of C20:0 FA induced a large accumulation in cellular lipids in peroxisome-deficient cells. Cytotoxic study of VLCFAs revealed that C20:0 FA exerted the highest toxicity toward peroxisome-deficient cells among tested C16-C26 FAs. I also found that the apoptotic effect of C20:0 FA was enhanced in the presence of a peroxisomal β-oxidation inhibitor in wild-type cells. There was a good positive correlation between the toxicity and extent of C20:0 FA accumulation in cellular lipids in these different conditions of experiments.</p> <p>These results suggest that peroxisome plays a pivotal role for getting rid of the cytotoxicity of accumulated VLCFAs, especially C20:0 FA. The knowledge obtained in these studies will contribute to a better understanding of the pathology of peroxisomal diseases.</p> | | | |