Department of Neuroscience
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General Summary

Our research projects have concerned neurodegenerative disorders caused by intracellular accumulation of abnormal proteins. We are also studying mouse models of neurodegenerative disorders and autopsy cases by means of standard morphologic analysis and molecular biological analysis.

Research Activities

Localization and dynamic changes of the MLC1 protein in the central nervous system
Mutations of the MLC1 gene are responsible for a form megalencephalic leukoencephalopathy with subcortical cysts (MLC). The function of the MLC1 protein is unknown. To characterize MLC1, we generated polyclonal antibodies against the MLC1 protein. The MLC1 protein and aquaporin 4 (AQP4) were expressed in the astrocyte end-feet membranes adjacent to blood vessels, the pia matter, and ependymal cells. In cerebral infarctions of spontaneously hypertensive/stroke-prone rats, we observed temporary loss of MLC1 and AQP4 during the edema phase and overexpression of them during the reactive astrocyte phase. Although a case of MLC examined at autopsy showed no mutation of MLC1 mRNA, a low expression level of MLC1 protein was shown by immunohistochemical study. MLC1 protein is suggested to have functions similar to those of AQP4, and further elucidation of the functions of MLC1 will be necessary to understand the precise molecular mechanisms whereby mutations of the MLC1 gene lead to myelin vacuolation.

Amyloid precursor proteins in spinocerebellar ataxia 7
Spinocerebellar ataxia 7 (SCA7) is a polyglutamine disease caused by polyglutamine expansion within a causative protein, ataxin-7. Recent evidence suggests that ataxin-7 regulates transcription and that aberrant regulation of transcription is related to the pathogenesis of SCA7; however, additional investigation is needed to clarify the pathogenesis of SCA7. Amyloid precursor-like protein (APLP) 2, a member of the amyloid precursor protein (APP) family, was identified as a partner protein of ataxin-7. We examined the subcellular distribution of APP-related proteins in SCA7 brains by immunohistochemical analysis.
Results: APP, APLP1, and APLP2 were localized mainly in the cytoplasm of normal control neurons. In SCA7 brains, nuclear APLP2 immunoreactivity was observed in neurons, although APP and APLP1 did not show clear nuclear localization. No neuronal intranuclear inclusions were immunostained with antibodies against APP,

APLP1, or APLP2. However, a few inclusions were immunostained with an antibody against caspase-cleaved APP/APLP proteins.

Discussion: The relation of the cleavage processes of APP or APLPs or both in the pathogenesis of Alzheimer disease has recently been demonstrated. Our data showing nuclear relocalization of APLP2 in SCA7 brains indicates that subcellular localization of APLP2 could be modified by the expression of mutated ataxin-7. In addition, recruitment of APP/APLPs caspase-3 cleavage products suggests that cleaved APP/APLPs might be enhanced in SCA7.

Publications

Fukumitsu N (Proton Med Res Ctr, Univ Tsukuba), Suzuki M, Fukuda T, Kiyono Y (Radioisotope Res Lab, Kyoto Univ), Kajiyama S (Dept Patho-Functional Bioanal, Kyoto Univ), Saji H (Dept Patho-Functional Bioanalysis, Kyoto Univ). Reduced ^{125}I-meta-iodobenzylguanidine uptake and norepinephrine transporter density in the hearts of mice with MPTP-induced parkinsonism. *Nucl Med Biol* 2006; **33:** 37–42.

Sato S[1], Chiba T[2], Nishiyama S[3], Kakiuchi T[3], Tsukada H[3] ([3]Central Res Lab, Mamamatsu Photonics), Hatano T[1], Fukuda T, Yasoshima Y[4], Kai N[4], Kobayashi K[4] ([4]Dept Mel Gen, Fukushima Med Univ), Mizuno Y[1], Tanaka K[2] ([2]Tokyo Metro Inst Med Sci), Hattori N[1] ([1]Dept Neurol, Juntendo Univ). Decline of striatal dopamine release in parkin-deficient mice revealed by *in vivo* autoradiography. *J Neurosci Res* 2006; **84:** 1350–7.

Kanai H, Marushima H, Kimura N, Iwaki T, Saito M, Maehashi H, Shimizu K, Muto M, Masaki T, Ohkawa K, Yokoyama K, Nakayama M, Harada T, Hano H, Hataba Y, Fukuda T, Nakamura M, Totsuka N, Ishikawa S, Unemura Y, Ishii Y, Yanaga K, Matsuura T. Extracorporeal bioartificial liver using the radial-flow bioreactor in treatment of fatal experimental hepatic encephalopathy. *Artificial Organs* 2007; **2:** 148–51.

Fukuda T, Arai T, Nikaido T, Joki T, Ikeuchi S, Kato M, Kawakami M, Abe T. A case of chordoid meningioma with allelic loss of 1p36. *Jikeikai Med J* 2006; **53:** 37–44.

Takahashi-Fujigasaki J, Fujigasaki H (Dep Neurol, Musashino Red Cross Hosp). Histone deacetylase (HDAC) 4 involvement in both Lewy and Marinesco bodies. *Neuropathol Appl Neurobiol* 2006; **32:** 562–6.

Yokoi K, Akiyama M, Yanagisawa T, Takahashi-Fujigasaki J, Yokokawa Y, Mikami-Terao Y, Fukuoka K, Fujisawa K, Nakazaki H, Oi S, Eto Y, Yamada H. Sequential analysis of cadherin expression in a 4-year-old girl with intracranial ependymoma. *Childs Nerv Syst* 2007; **23:** 237–42.

Arai T, Tani S, Isoshima A, Nagashima H, Joki T, Takahashi-Fujigasaki J, Abe T. Intraoperative photodynamic diagnosis for spinal ependymoma using 5-aminolevulinic acid: technical note. *No Shinkei Geka* 2006; **34:** 811–7.

Mikami-Terao Y, Akiyama M, Yanagisawa T, Takahashi-Fujigasaki J, Yokoi K, Fukuoka K, Sakuma M, Miyata I, Fujisawa K, Oi S, Eto Y. Lymphocytic hypophysitis with central diabetes insipidus and subsequent hypopituitarism masking a suprasellar germinoma in a 13-year-old girl. *Childs Nerv Syst* 2006; **22:** 1338–43.