Laboratories
Neuropathology

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General Summary

Our research projects have concerned neurodegenerative disorders caused by the 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

Caspase independent apoptosis in the central nervous system in mouse models of prosaposin deficiency disease

Introduction: The pathophysiological changes of the central nervous system (CNS) in prosaposin knockout mice accompanies the degeneration of neurons and axons with organelle changes and the activation of ubiquitin-proteasome and autophagy-lysosome systems. In the CNS of prosaposin knockout mice 9 to 31 days old, the number of subunit c of mitochondria ATP synthase (SCMAS)-immunoreactive neurons increases in proportion to the number of amino-cupric-silver-impregnated neurons. However, caspase-dependent apoptosis has not been evaluated with active caspase 3 immunohistochemistry and the terminal deoxyribonucleotidyl transferase-mediated deoxyuridine triphosphate-biotin fluorescein nick-end labeling (TUNEL) method. Although much emphasis has been laid on the role of caspase in cell death, recent data indicate that, in many instances, mammalian cell death is caspase-independent. Apoptosis-inducing factor (AIF) is a new mammalian, caspase-independent death effector which, upon apoptosis induction, translocates from its normal localization, the mitochondrial intermembrane space, to the nucleus. Once in the nucleus, AIF causes chromatin condensation and large-scale DNA fragmentation to fragments of approximately 50 kbp. This study investigated the AIF in the CNS of prosaposin knockout mice using anti-AIF antibodies.

Material and methods: We analyzed the central CNS of mouse models of prosaposin deficiency with the amino-cupric-silver method and immunohistochemical methods with antibodies against SCMAS and AIF.

Results: From 8 days of age, the neurons of the spinal cord, brain stem, deep cerebellar gray matter, diencephalon, striatum, and cerebrum in prosaposin knockout mice immunoexpressed SCMAS in proportion to the amino-cupric-silver-impregnated neurons. Subsequently, the distribution of SCMAS immunoreactive and the amino-cupric-silver-impregnated neurons spread in the CNS in general. The AIF migrated into the nuclei of neurons in the spinal cord, brainstem nuclei, deep cerebellar gray matter, and striatum from 21 days of age and was persistently expressed in the nuclei from approximately 30 days of age until death.

Discussion: In the CNS neurons of prosaposin knockout mice, swollen lysosomes accumulated. The number of structurally preserved peroxisomes and Golgi apparatuses decreased slightly. In contrast, the number of mitochondria, endosomes, endoplasmic reticulum, and ribosomes decreased markedly. After sorting in endosomes, most of the proteins are rapidly recycled. Degraded proteins are packaged into lysosomes and then processed into ubiquitin-proteasome system or autophagy-lysosome system. In lysosomal storage diseases, recycled endosomes were inhibited and degraded proteins accumulated in the lysosomes. Mitochondria depletion developed the energy crisis and decreased the activity of protein and lipid synthesis in ribosomes and endoplasmic reticulum.
We also reported the accumulation of SCMAS in the neuronal cytoplasm of neuronal ceroid lipofuscinoses; mucopolysaccharidoses types I, II, and VII; Niemann-Pick disease type C; Fabry disease; mucolipidoses; and methylenetetrahydrofolate reductase deficiency and that SCMAS is a candidate for amino-cupric-silver-impregnated material in the CNS of prosaposin knockout mice. The increase of ATP synthase might be induced by the depletion of ATP because of the organelles' dysfunction and the activations of ubiquitin-proteasome and autophagy-lysosome systems. However, caspase-dependent apoptosis has not been evaluated with active caspase 3 immunohistochemistry and the TUNEL method. The AIF is released from mitochondria during cell death and migrates into the nucleus and might be involved in DNA aggregation and fragmentation in a mouse model of prosaposin deficiency disease.

Publications

Kawamura M, Sato S, Matsumoto G, Fukuda T, Shiba-Fukushima K, Noda S, Takanashi M, Mori N, Hattori N. Loss of nuclear REST/NRSF in aged-dopaminergic neurons in Parkinson's disease patients. *Neurosci Lett.* 2019 Apr 23; **699**: 59-63. doi: 10.1016/j.neulet.2019.01.042. Epub 2019 Jan 23. PubMed PMID: 30684677.

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