

Dementia and Alzheimer's Disease

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Vegetable oil-derived hydroxynonenal causes Alzheimer's neuronal death via Hsp70.1 depletion

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Recent data advocate for dual roles of heat-shock protein 70.1 (Hsp70.1) not only as a molecular chaperone for altered proteins but also as a guardian of lysosomal integrity. Thus, in case of Hsp70.1 dysfunction, not only failure of protein traffic and degradation but also lysosomal destabilization may occur. In the monkey hippocampal CA1 neurons after transient ischemia, the author's group previously found by proteomic analysis that Hsp70.1 can become an in-vivo target of carbonylation by a lipid peroxidation product, hydroxynonenal (HNE). Furthermore, in the in-vitro experiments Hsp70.1 carbonylated by HNE was found to be susceptible to cleavage by activated μ -calpain. Calpain-mediated Hsp70.1 cleavage can lead to autophagy failure and lysosomal destabilization with the resultant release of cathepsins and neuronal death. Focusing this 'calpain-cathepsin hypothesis', I summarize current advance on ischemic neuronal death, and forward a perspective view that the causative substance for Alzheimer neuronal death is actually 'vegetable oils'. Targeting especially $\omega=6$ PUFA (poly-unsaturated fatty acid)-derived HNE may help elucidate the pathogenesis of Alzheimer's disease.

Speaker Biography

Tetsumori Yamashima is a consultant neurosurgeon specialized in neuroscience. In 1975, he graduated from Kanazawa University Faculty of Medicine. In 1979, he completed his research diploma in the Kanazawa University Graduate School Medical Research Course (Doctor of Medicine). He then studied abroad in Germany and Sweden, including neuropathology and brain science. He became Chief of Medical Staff at Kanazawa University Hospital, Associate Professor of Kanazawa University Medical Faculty, and Director of Restorative Neurosurgery at Kanazawa University Graduate School of Medical Science. At present, he is CEO of the Arimatsu Medical and Dental Clinic in Kanazawa city, works at this clinic (Tuesday to Saturday), and at Minami-gaoka Hospital (consultant neurosurgeon: Monday mornings). At Kanazawa University Hospital (part-time lecturer: Monday afternoons), he heads a special "higher brain dysfunction" outpatient clinic. He is acknowledged for using the RBANS (Repeatable Battery for the Assessment of Neuropsychological Status), MRI and PET scans for early detection of Alzheimer's disease, even a few years before dementia appears, allowing preventive treatment to be carried out. In 1998, he proposed the "calpain-cathepsin hypothesis" as a mechanism of neuronal cell death. He also discovered that the causative agent responsible for Alzheimer's disease is not amyloid β , but hydroxynonenal derived from "cooking oil". He is the author of 200 published scientific papers in English, and 75 papers and 15 books in Japanese.

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