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

Tetsumori Yamashima
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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 ω=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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The lived experience of older migrants with mild cognitive impairment

Ray Jauny
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Mild cognitive impairment (MCI) is a complex intermediate state of memory decline which is widely known as a precursor to Alzheimer's disease (AD). However, not all those diagnosed with MCI progress to AD, though many remains cognitively impaired for life, but many recovers completely from it. MCI is an emerging primary target of aging research among older population. It is well-known that MCI may have significant impact on older migrants' health, which can mean disengagement from activities, isolation, social disconnection, poor quality of life, and results in considerable socio-economic burden. Older migrants, are ethnically, culturally and linguistically diverse and are predisposed to develop psycho-social distress, loneliness, trauma and physical health complications. Cultural factors, language barriers, and the resettlement process can also affect cognitive functioning of older migrants.

Aim: This research will provide valuable information to better understand the lived experiences of older migrants with MCI in New Zealand. Research into their lived experience will help shape up strategies to support longer and better-quality life. Better understanding of MCI is imperative to improve its awareness, enhance professional practice and helps deliver quality health services.

Method: Purposively sampled community-dwelling older migrants, diagnosed with MCI, who are 55 years old and over, will be recruited in Auckland's region, to participate in semi-structured interviews. Data will be inductively interpreted through a phenomenological lens. This methodology helps to penetrate deeper and deeper into the reality of the world as it is experienced by older migrants.

Discussion: This research provides a wealth of knowledge on older migrants' experience of MCI. It is anticipated that learning from this research will help reduce a gap in knowledge, help change practice and offer a culture-specific outcomes on improving the health of older migrants.

Speaker Biography

Ray Jauny is the course coordinator/lecturer for mental health nursing at Unitec Institute of Technology in Auckland. Ray has an extensive variety of experience in mental health settings in New Zealand and the UK. He is an academic leader and a new emerging researcher in health sciences. Ray is currently doing his doctoral studies at Auckland Institute of Technology. His main research interests relate to the health and well-being of communities, particularly older populations, older migrants, delirium, mood self- assessment application tool and as well as nurses' attitudes towards end of life choice. He has published articles and presented to conferences.

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A systematic review and meta-analysis of the effect of melatonin, melatonin agonist and melatonin precursor on delirium prevention in the elderly medical and surgical inpatients

Kay Khaing
Hunter New England Health NSW, Australia

Background and aims: Melatonin is a pineal gland hormone synthesised within the pinealocytes. It is believed to have a protective effect against delirium. This study aimed to investigate the effects of melatonin, melatonin receptor agonist and melatonin precursor on delirium prevention in the elderly medical and surgical patients.

Methods: Controlled trials of melatonin, melatonin agonist (ramelteon) and melatonin precursor (tryptophan) were included. A meta-analysis with a random effects model was performed.

Findings: 7 studies (1515 participants) met the inclusion criteria. Among medical patients, delirium risk reduced by 63% with Melatonin, 88% with Ramelteon and insignificantly with tryptophan. Hallucination and nightmare were more prevalent in patients taking melatonin.

Interpretation: Ramelteon and Melatonin were associated with a fall in delirium incidence. But its benefit needs to be balanced against its potential side effects of hallucinations and nightmares.

Speaker Biography

Kay Khaing has completed MBBS at the age of 25 years from Institute of Medicine 2, Yangon, Myanmar and Master of Medicine (Clinical Epidemiology) from University of Sydney in 2016. She has completed Geriatric Fellowship in 2017 and is working as a Geriatrician

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Loss-of-function mutation in RUSC2 causes ntellectual disability and secondary microcephaly

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Intellectual disability is seen in up to 1% to 3% of the general population, and is often dichotomized into syndromic and non-syndromic forms. A genetic aetiology accounts for about 25% to 50% of cases, with up to 700 monogenic mutations identified so far. Recent advances in genetic testing have allowed the identification of an ever-increasing repertoire of genes causing intellectual disability. Characterization of their protein products has shed light onto the diverse biological pathways affected in this important neurological disease that results in significant impairment in cognitive and adaptive behaviour, and which has important medical and social implications. Aberrancies in synaptic vesicular transport and intracellular protein trafficking have been highlighted among the various biological pathways reported to cause intellectual disability. Included in these are mutations in genes coding for Rab proteins (rabaptins), a group of small Ras GTPases that have been shown to play an important role at different levels of the cellular trafficking pathway. Although over 60 Rab proteins have been identified so far, only a few have been implicated in human disease, including in patients with intellectual disability with or without associated brain malformations. RUSC2, officially known as RUN and SH3 domain containing a gene found on chromosome 9p13.3 (gene identifier [ID] 9853, Mendelian Inheritance in Man [MIM] 611053). RUSC2 codes for iporin, a ubiquitous protein with moderate to high expression in the human brain. The literature on the functions of iporin remains sparse, but there is some evidence that it interacts with Rab1b and Rab1-binding protein GM130,10 both of which are also expressed in the brain, with highest expression in dendritic spines where they appear to play an important role in synaptogenesis. So far, no mutations in RUSC2 have ever been shown to cause human disease, and no animal models disrupting this gene have been described. However, to our knowledge for the first time, we describe the clinical presentations of three patients (two male siblings and one unrelated female) with severe intellectual disability and microcephaly. Through whole-exome sequencing, all three were found to have inherited homozygous nonsense mutations in RUSC2.

Speaker Biography

Ali H Alwadei currently works at Pediatric Neurology Department, National Neuroscience Institute, King Fahad Medical City, Saudi Arabia.

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Electric axon guidance in embryonic retina: Involvement of integrins

Masayuki Yamashita
Center for Medical Science, Japan

The axons of embryonic brain, spinal cord, and retina extend along the extracellular voltage gradient towards the cathode in a process known as galvanotropism. In embryonic nervous tissues, positive direct current (DC) potentials are generated by neuroepithelial cell's sodium transport1, of which disruption results in erroneous axon path-finding4, suggesting that electric fields play a pivotal role in orienting newborn axons. However, the experimental evidence was lacking for the cell surface molecule that is activated asymmetrically in an electric field. Here I show that integrin activation mediates electric axon guidance. Retinal strips of chick embryos were embedded in Matrigel®, and cultured in the electric field of the same strength as that in vivo (15 mV/mm)4. Matrigel® contained the same extracellular matrix proteins as in the embryonic retina, laminin and collagen, to which integrins bind. Retinal ganglion cell axons extended towards the cathode2. A monoclonal anti-chicken integrin antibody (TASC), which enhances integrin-ligand binding, accelerated the cathodal growth. A reduction in the extracellular free Ca2+ with EGTA also enhanced the cathodal growth, which suggested that millimolar Ca2+ inhibits axon growth, and also that the influx of Ca2+ was unlikely to be essential for cathodal steering. In the presence of Mn2+, which non-specifically activates integrin-ligand binding, the axons formed local meshes. These results suggested that the inhibition of integrins by the extracellular Ca2+ underlies electric axon guidance.

Recent Publications:

1. Yamashita M (2016) Epithelial sodium channels (ENaC) produce extracellular positive DC potentials in the retinal neuroepithelium. Data in Brief, 6: 253-256.

2. Yamashita M (2015) Weak electric fields serve as guidance cues that direct retinal ganglion cell axons in vitro. Biochemistry and Biophysics Reports, 4: 83-88.

3. Yamashita M (2015) Electrophysiological recordings from neuroepithelial stem cells. Stem Cell Renewal and Cell-Cell Communication (Ed. Turksen K), Methods in Molecular Biology, Springer Protocols, 1212: 195-200.

4. Yamashita M (2013) Electric axon guidance in embryonic retina: Galvanotropism revisited. Biochem Biophys Res Commun, 431: 280-283.

5. Yamashita M (2013) From neuroepithelial cells to neurons: Changes in the physiological properties of neuroepithelial stem cells. Arch Biochem Biophys, 534: 64-70.

6. Yamashita M (2012) Ion channel activities in neural stem cells of the neuroepithelium. Stem Cells International, 2012: doi: org/10.1155/2012/247670.

Speaker Biography

Masayuki Yamashita is a professor of physiology at International University of Health and Welfare. He received his PhD at the Department of Neurophysiology, Institute of Brain Research, School of Medicine, University of Tokyo in 1986. He moved to National Institute for Physiological Sciences (Okazaki, Japan) as a JSPS fellow and a research associate. In 1989, he started physiological studies of retina at the Department of Neuroanatomy, Max-Planck-Institute for Brain Research (Frankfurt/M). After the reunification of Germany, he moved to the Department of Physiology, Osaka University Medical School. He studied the calcium signaling systems in embryonic chick retina. Then, he moved to the Department of Physiology, Nara Medical University as a professor (1999-2014). He has been interested in the electrophysiological properties of neuroepithelial cells and newborn neurons. The retina is a nice model for studying the early development of central nervous systems.

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