Title of Research:23-6-03

A Validation Study for approval of AOP475 that proposes a New Approach Method for OECDTG on Neurotoxicity and Developmental Neurotoxicity

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Summary of Research:

The aim of this research is to further validate and finalize the AOPwiki entry for AOP475 proposed to the OECD. During this term, we continued strengthening the scientific basis of the Key Events (KEs) and Key Event Relationships (KERs) through literature analysis and experimental validation. In addition to the previously described events, we incorporated new KEs including **Loss of drebrin** and **dendritic spine abnormality**, which describe a pathway leading to impairment of learning and memory without neuronal cell death. Experiments using frozen rat hippocampal neurons for primary culture were conducted to examine the relationship between receptor activation, intracellular calcium signaling, and drebrin loss. Activation of NMDA receptors and kainate receptors induced a reduction of drebrin clusters in dendritic spines, even under conditions that did not necessarily cause neuronal cell death. Furthermore, experiments using a calcium ionophore demonstrated that intracellular calcium overload can trigger drebrin loss independently of calpain-mediated neuronal death. In addition, a clinical study using the ELISA-based drebrin quantification method (Syncheck™) revealed that drebrin degradation products in human plasma are significantly decreased in patients with mild cognitive impairment. These findings support the human relevance of AOP475 and suggest that changes in drebrin localization and expression can serve as useful indicators for the risk assessment of compounds affecting learning and memory.

Timeline:

March 2025 – February 2026

Topics:

Presented at the LRI annual research meeting of JCIA. August 29, 2025.
Three at Society for Neurochemistry (11^{th}-12^{th} Sept.2025),
One at Society for Regulatory Science (5^{th}-6^{th} Oct.2025)
Press release on the web site of Univ. Tokyo on 7^{th} Jan. in 2026

Publications:

[Original paper] Shoji M, Kawarabayashi T, Nakamura T, Sugawara T, Ishizawa K, Amari M, Takahashi R, Kasahara H, Koganezawa N, Higa A, Takatama M, Ikeda Y, Sekino Y, Shirao T. Drebrin is a novel biomarker of cognitive deterioration in Alzheimer's disease. J Alzheimers Dis. 2026 Feb;109(4):1824-1833.