

Hepatic Ceramide Content In The Liver And The Brain Associates With Neuroinflammation In Male APP/PS1 Mice

Carlos Alfredo Silva Ramírez, MS, Pablo Muriel, PhD, and Claudia Perez-Cruz, PhD*
*Center of Reseach and Advanced Studies (CINVESTAV), Mexico City, Mexico.

KEY TAKE AWAY
AD transgenic mice develop altered lipid metabolism in the liver, associated with enhanced accumulation of ceramides in this organ and in the brain. Ceramide content may be related to an enhanced neuroinflammation in the hippocampus (*stratum radiatum*).

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS
It is known that lipid accumulation in the liver leads to metabolic-associated steatotic liver disease (MASLD), a pathology that has been associated with Alzheimer's disease (AD). MASLD relates to alterations in lipid metabolism in several organs, including the brain. Impaired lipid metabolism in the brain leads to synthesizing toxic compounds, such as ceramides. Ceramides are sphingolipids composed of a fatty acid with a variable chain length, and an amino group (sphingosine). Ceramide accumulation in the brain is associated with enhanced neuroinflammation. However, it is unknown if APP/PS1 mice develop alterations in lipid metabolism in the liver and whether this alteration may be associated with ceramide accumulation and neuroinflammation in the brain.	Animals 6-month-old Wild-type (WT) APP/PS1 (TG) Experimental design Liver ELISA detecting ceramide Brain Oil Red-O staining Immunohistochemistry Immunofluorescence Image acquisition and analysis	APP/PS1 mice show a higher lipid and ceramide accumulation in liver than WT mice WT TG ORO staining WT TG Ceramide-IHC APP/PS1 mice show an enhanced ceramide content in the hippocampus WT TG Stratum Radiatum APP/PS1 mice brains exhibit an increased astrocyte density WT TG Stratum Radiatum GFAP+ astrocytes co-localise with ceramide in the hippocampus (<i>stratum radiatum</i>)	APP/PS1 mice exhibit an altered lipid metabolism and enhanced accumulation of ceramides in the liver and in the brain. In the hippocampus, ceramides were accumulated in GFAP+ astrocytes in APP/PS1 mice, but not in WT controls. Our results provide insight into lipid metabolic alterations that may be associated with the onset of AD pathology, with particular emphasis on the liver-brain axis, as previously described in several studies (1, 2, 3). SUPPORT Supported by CINVESTAV and SECIHTI fellowship #4041340 REFERENCES 1. den Hoedt, S., Crivelli, S. M., Leijten, F. P. J., Losen, M., Stevens, J. A. A., Mané-Damas, M., de Vries, H. E., Walter, J., Mirzaian, M., Sijbrands, E. J. G., Aerts, J. M. F. G., Verhoeven, A. J. M., Martinez-Martinez, P., & Mulder, M. T. (2021). Effects of Sex, Age, and Apolipoprotein E Genotype on Brain Ceramides and Sphingosine-1-Phosphate in Alzheimer's Disease and Control Mice. <i>Frontiers in Aging Neuroscience</i>, 13. https://doi.org/10.3389/fnagi.2021.765252 2. Liu, X., Jin, Y., Cheng, X., Song, Q., Wang, Y., He, L., & Chen, T. (2024). The relevance between abnormally elevated serum ceramide and cognitive impairment in Alzheimer's disease model mice and its mechanism. <i>Psychopharmacology</i>. https://doi.org/10.1007/s00213-024-06530-y 3. Sato, H., Tomimoto, H., Ohtani, R., Kitano, T., Kondo, T., Watanabe, M., Oka, N., Akiguchi, I., Furuya, S., Hirabayashi, Y., & Okazaki, T. (2005). Astroglial expression of ceramide in Alzheimer's disease brains: A role during neuronal apoptosis. <i>Neuroscience</i>, 130(3), 657–666. https://doi.org/10.1016/j.neuroscience.2004.08.056 CONTACT Claudia Perez-Cruz Pablo Muriel Carlos Alfredo Silva-Ramírez cperezc@cinvestav.mx pmuriel@cinvestav.mx carlos.silva@cinvestav.mx ALZHEIMER'S ASSOCIATION AAIC 26