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Regulation of Tau Hyperphosphorylation by miR-15a and Manganese via MAPK3/ERK1 Pathway

In neurodegenerative Alzheimer's disease (AD), the extracellular aggregation of beta-amyloid protein (AßP) into senile plaques (SPs), and the intracellular aggregation of hyperphosphorylated tau protein into neurofibrillary tangles (NFTs)[1,2,3,4] in the hippocampus and neocortex[5] are prominent pathological features. In these areas of the brain prone to AD protein accumulation, elevated levels of the endogenous metals zinc, copper and iron[5] have been found as well as unusual and contradictory levels of the exogenous metal aluminum.[4] Interestingly, altered microRNA (miRNA) levels have also been found in the neocortex[6,7] and hippocampus[8,9] of AD patients. Furthermore, it has been observed that metal salts can initiate similar changes in miRNA level of cultured neuronal cells.[8]

Independent studies have indicated that both manganese (II) ions[10] and miR-15a[11] initiate tau hyperphosphorylation through the ERK1/MAPK3 pathway, but the relationship between manganese salt treatment and miR-15a levels so far remains unknown. In order to understand this relationship between manganese (II) ions and miR-15a, we began by creating a luciferase MAPK3 reporter construct with a miR-15a binding sequence from the MAPK3 3'UTR. This construct will allow for the quantification of MAPK3 expression in transfected BE(2)-C and SHSY-5Y neuronal cell lines under varying concentrations of manganese metal salt solutions and miR-15a. Due to the synergistic effects observed between metals in neural cell lines,[12] and evidence that manganese accumulation in the brain leads to changes in dietary iron levels,[13] varying concentrations of iron, zinc and aluminum salt solutions were also applied to BE(2)-C cells when observing MAPK3 variation. In order to also study the expression of miR-15a in response to various metal treatments, GFP reporter constructs were designed with miR-15a inserts. These miR-15a constructs will be transfected into neuronal cell lines and the levels of miR-15a quantified under various metal conditions. Once correlations have been identified in miR-15a and MAPK3 levels from metal treatment, we will use Western Blotting Techniques to further quantify expression of MAPK3 under various metal and miRNA conditions.

1. 5. Haddad, J. J., Mitogen-activated protein kinases and the evolution of Alzheimer's: a revolutionary neurogenetic axis for therapeutic intervention? Prog. Neurobiol. (Amsterdam, Neth.) 2004, 73, (5), 359-377.
2. 9. Obulesu, M.; Venu, R.; Somashekhar, R., Tau Mediated Neurodegeneration: An Insight into Alzheimer's Disease Pathology. Neurochem. Res. 36, (8), 1329-1335.
3. 12. White, A. R.; Reyes, R.; Mercer, J. F. B.; Camakaris, J.; Zheng, H.; Bush, A. I.; Multhaup, G.; Beyreuther, K.; Masters, C. L.; Cappai, R., Copper levels are increased in the cerebral cortex and liver of APP and APLP2 knockout mice. Brain Res. 1999, 842, (2), 439-444.
4. 13. Zatta, P.; Drago, D.; Bolognin, S.; Sensi, S. L., Alzheimer's disease, metal ions and metal homeostatic therapy. Trends Pharmacol. Sci. 2009, 30, (7), 346-355.
5. 2. Bush, A. I., The metallobiology of Alzheimer's disease. Trends in Neurosciences 2003, 26, (4), 207-214.
6. 10. Sethi, P.; Lukiw, W. J., Micro-RNA abundance and stability in human brain: Specific alterations in Alzheimer's disease temporal lobe neocortex. Neurosci. Lett. 2009, 459, (2), 100-104.
7. 11. Wang, W.-X.; Huang, Q.; Hu, Y.; Stromberg, A.; Nelson, P., Patterns of microRNA expression in normal and early Alzheimer's disease human temporal cortex: white matter versus gray matter. Acta Neuropathologica 121, (2), 193-205.
8. 7. Lukiw, W. J.; Pogue, A. I., Induction of specific micro RNA (miRNA) species by ROS-generating metal sulfates in primary human brain cells. J. Inorg. Biochem. 2007, 101, (9), 1265-1269.
9. 8. Nelson, P. T.; Wang, W.-X.; Rajeev, B. W., MicroRNAs (miRNAs) in neurodegenerative diseases. Brain Pathol. 2008, 18, (1), 130-138.
10. 3. Cai, T.; Che, H.; Yao, T.; Chen, Y.; Huang, C.; Zhang, W.; Du, K.; Zhang, J.; Cao, Y.; Chen, J.; Luo, W., Manganese Induces Tau Hyperphosphorylation through the Activation of ERK MAPK Pathway in PC12 Cells. Toxicol. Sci. 119, (1), 169-177.
11. 6. Hebert, S. S.; Papadopoulou, A. S.; Smith, P.; Galas, M.-C.; Planel, E.; Silahtaroglu, A. N.; Sergeant, N.; Buee, L.; De, S. B., Genetic ablation of Dicer in adult forebrain neurons results in abnormal tau hyperphosphorylation and neurodegeneration. Hum. Mol. Genet. 19, (20), 3959-3969.
12. 1. Alexandrov P. N.; Zhao, Y.; Pogue A. I.; Tarr, M. A.; Kruck, T. P. A.; Percy, M. E.; Cui, J.; Lukiw,W. J., Synergistic effects of iron and aluminum on stree-related gene expression in primary human neural cells. J. Alzheimers Dis. 2005, 8, (2), 117-127.
13. 4. Fitsanakis A. V.; Zhang, N.; Avison, M. J.; Erikson, K. M.; Gore, J. C.; Aschner, M., Changes in Dietary Iron Exacerbate Regional Brain Manganese Accumulation as Determined by Magnetic Resonance Imaging. J. Toxicol. Sci. 2011, 120, (1), 146-153.