EFFECTS OF MATRIX METALLOPROTEINASE-9 ON INSULIN SURVIVAL PATHWAYS IN ALZHEIMER'S DISEASE

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Defective brain insulin signaling has been suggested to contribute to the cognitive deficits in patients with Alzheimer's disease (AD). Although a connection between AD and diabetes has been suggested, the mechanism(s) by which insulin resistance in the brain arises in individuals with AD remains to be elucidated. One of the hallmarks of AD is the abnormal accumulation of amyloid-β (Aβ) peptide, the oligomeric form of which is believed to be primarily responsible for cell toxicity and neuronal dysfunction in various experimental models of AD, as well as in AD patients. Interestingly, insulin signaling provides a physiological defense mechanism against oligomer-induced synapse loss. We have previously reported that matrix metalloproteinase 9 (MMP9), an enzyme critically involved in neuronal plasticity, appears to have a neuroprotective role by acting as α-secretase and by decreasing the formation of Aβ. To elucidate the role of MMP-9 on insulin survival pathways in AD, we will examine possible alterations in the proteins involved in the insulin pathway, such as nephrin and insulin receptor substrate -1 and -2 (IRS1, IRS2). Our preliminary experiments suggest that there is no difference in the expression levels of IRS1/2 in mice overexpressing MMP9 in the CNS (TgMMP9), mouse models of AD (5XFAD) and double transgenic animals 5XFAD/TgMMP9, compared to controls. However, since differences are expected in the phosphorylation of IRS1, IRS2 we investigated possible changes in primary hippocampal cultures; overall, we observed an increase in IRS1 expression concomitantly with a downstream increase in AKT phosphorylation, in transgenic mice compared to controls. Moreover, we examined by RT-PCR and confocal imaging the expression levels of survival-associated nephrin in primary cultures; we also observed an increase in nephrin expression in transgenic animals, compared to control mice. Further investigation is required to elucidate the role of MMP9 with regards to the insulin survival pathway.