**Alzheimer’s disease: Insulin- Degrading Enzyme**

**Abstract**

A closer focus is being done as to why the progression of Alzheimer’s disease occurs after years of research. There has been no luck on the aspect. One factor that is major to the cause of Alzheimer’s disease is impaired clearance of amyloid beta peptides. Yet it was recently complemented by a potential role of other toxic amyloidogenic species (Kurochkin, 2017). Insulin-degrading enzyme is the proteolytic culprit of carious B-forming peptides, both extracellular and intracellular (Kurochkin, 2017).

**Introduction**

Alzheimer’s disease is an illness of the brain that insidiously and steadily robs a person of his or her mental abilities. This affects millions of people and ranges from ages 45 or older. Standing at archetypal molecular pathology point associated with Alzheimer’s disease is the accumulation of amyloid plaques in the brain, consisting of the amyloid beta peptide, and neurofibrillary tangles composed of hyper phosphorylated tau protein (Kurochkin, 2017). The amyloid cascade hypothesis, that AB deposition in the brain drives the sequence of pathogenic events. This will then lead to Alzheimer’s (Kurochkin, 2017). This serves, as an endowment of the development of drugs against Alzheimer’s to earmark the production of AB or more so to remove the AB deposits. All trials had failed to show potency of the antiamyloid therapies. One main factor that leads to synaptic and neuronal dysfunction is the accumulation of intraneuronal AB, which foregoing deposits both NFTs and extracellular AB plaque. Suggested that oligomeric forms of AB are the primary toxic species that can cause synaptic damage and neurodegeneration, constituting so-called amyloid hypothesis (Kurochkin, 2017).

**Recent Progress**

Yet another hypothesis was implied known as the N-terminal hypothesis as it implicates N-terminally extended domain of neurotoxic AB in causing disease. A number of polypeptide with a potential to assemblage into toxic oligomers can be accumulated over time in the aging brain, which leads to the degeneration of neuron cells.

Assorted cleansing systems can be done in the dismissal of soluble AB, such as extracellular and intracellular in the blood via the blood-brain barrier. Even though AB is discharged from the cell upon construction from amyloid precursor protein. Among several proteases degrading the AB in vitro, only neprilysin and insulin-degrading enzyme play a notable role in extracellular and intracellular AB degradation (Kurochkin, 2017). A main contributor against toxic oligomers is the IDE, which is only towards B-structure establishing substrates. This leads to the degeneration of neuron cells. However, Neprilysin has a broad substrate specificity, hewing peptides on the N-terminal side of the residues that are hydrophobic. Since the recognition of IDE, it has been shown that it is the major protease responsible for AB removal in human hippocampal lysates and for the debasement of AB in the cytoplasm and cerebrospinal fluid (Kurochkin, 2017). IDE can also be found in other cellular compartments other than the major location, which is the cytosol. IDE is presence in more areas such as blood, exosomes, endosomes, and also transport outside of cells. Now how IDE correlates more so with Alzheimer’s regulates the AB levels. When the concentration of IDE is decreased, these will ignite the progression of Alzheimer’s. Many studies had reported the association between the risk of genetic variation in IDE and Alzheimer’. Another aspect where the IDE expression is induced from AB is suggested an important feedback mechanism aiming at bringing down the levels of toxic peptides(Kurochkin, 2017). The IDE levels elevate after first AB plaques development within the cortex of Alzheimer’s transgenic mouse model. Resulted in increased level of IDE expression that was detected by AB fibrillar depostis within the glibal fibrillar acidic protein- positive astrocytes in the aged APP-transgenic mice (Kurochkin, 2017). IDE happens to be an active enzyme, which goes under oxidation that results in the loss of its activity. A linkage was found between type 2 diabetes and Alzheimer’s as they share common features between pathologies. One major factor was identified as inhibition of the brain IDE. This has increased levels of glucose result in a significant rise in a significant rise neuronal reactive nitrogen species, causing the aberrant S-nitrosylation of IDE and decreasing its activity(Kurochkin, 2017). Which then detected that there was higher levels of S-nitroslyated IDE were found in Alzheimer’s brains than in the same age range.

**Discussion**

To conclude on this unsuccessful outlook on the progression of Alzheimer’s, do these hypotheses correlate to all patients? Do these hypotheses correlate to all patients, since majority of them run through different stages and at different rates on a molecular and cellular level? Hopefully in the near future there will be more technology to look into this complex disease and find preventions.

# References

Kurochkin, i. V., Guarnera, E., & Berezovsky, I. N. (2017, 11 10). *Web of science*. Retrieved from Science direct: https://www.sciencedirect.com/science/article/pii/S0165614717302031