

INHIBITION OF INSULIN AMYLOID FORMATION BY SMALL ORGANOFLUORINE MOLECULES

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Many human diseases, including Alzheimer's disease (AD) and diabetes mellitus type II (DM) have been connected to protein misfolding and the formation of highly ordered fibrillar protein aggregates called amyloids. DM is characterized by an overproduction of insulin to the point of insulin resistance in the body. The protein deposits in the AD-affected brain is related to the aggregation of tau protein and amyloid β (A β) peptide. Amyloid fibrils and their oligomeric precursors are known to be cytotoxic inducing neurological cell death. Recent clinical studies have suggested a link between Alzheimer's disease and DM based on the fact that DM patients have double the risk of developing Alzheimer's disease. It is believed that the increased risk of heart disease and stroke linked to DM causes further damage to blood vessels that eventually target the brain. Due to the continued rise of both diseases among aging adults, there is considerable interest in elucidating the similarities and differences in the mechanism of amyloid formation of insulin and A β and understanding how the oligomeric state of the two peptides affect each other's aggregation and role. Our group has already designed and experimentally tested a broad variety of small molecules, including organofluorines that effectively inhibit the self-assembly of A β . As an extension of these earlier studies the same group of organofluorine molecules are being tested for their inhibitory activity in the formation of insulin fibrils. The aggregation of insulin with/without these potential inhibitors at 37°C and pH=7.4 are followed by a kinetic Thioflavin T (ThT) fluorescence assay and visualized by Atomic Force Microscopy (AFM). The small molecule-insulin interactions are also investigated by electrospray mass spectrometry (HR-ESI-MS).

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