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Intranasal delivery of insulin for the restoration of memory signaling in Alzheimer disease

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Objectives: Alzheimer's disease(AD), a form of dementia, is a progressive, degenerative brain disease characterized by marked atrophy of cerebral cortex and loss of cortical and sub-cortical neurons. Weakening of insulin receptor signaling is involved in ageing-related brain degeneration such as AD. Objective of study is to develop a delivery-system to overcome BBB by employing novel, non-invasive approach via nasal route. The olfactory neural pathway provides both intraneuronal and extraneuronal pathway into brain. In present study delivery of antibody appended Insulin encapsulated carrier, PEGylated nanoparticle coated with chitosan to facilitate nasal absorption for efficient transfer to brain.

Methods: PEGylated-PLGA nanoparticles were prepared by modified Double Emulsification method and coated with chitosan by freeze drying. Characterization was done by FTIR, NMR, *in-vitro* for shape, size, and drug entrapment. *In-vivo* study comprised biodistribution in various organs and fluorescence microscopy, estimation of Anti-A β antibody, PET-Imaging of Brain, Hemolytic Toxicity studies, Histopathology of Nasal Mucosa and Brain with periodic Blood Glucose Level Monitoring.

Results: Nanoparticles were spherical in shape and smooth. Degree of hemolysis showed PEGylated(PEG-NP's) and chitosan coated nanoparticles(cPEG-NP's) were less toxic. Blood glucose monitoring indicates reduction in blood glucose level in cPEG-NP's. Biodistribution assessment suggests nanoparticles showed maximum availability at olfactory bulb entrance. Chitosan coating increased CSF availability of drug even at initial period of administration. Uptake study shows intense fluorescence in brain revealing higher uptake of nanoparticles. These studies highlight possible biological significance of cPEG-NP's for delivery to brain.

Conclusions: Results from various studies suggest nanoparticles are effective delivery system for targeted delivery of insulin in brain for extended period. Coating with chitosan elicits associated benefits in addition to prolonging uptake via intranasal route. This project provides sound platform towards employment of this modified nanoparticulate carrier for brain delivery of proteins and peptides towards intranasal delivery of insulin for restoration of memory signaling in Alzheimer patients.