Brain insulin resistance

Targeting brain insulin resistance (BIR) has become an attractive alternative to traditional therapeutic treatments for Alzheimer's disease (AD). Incretin receptor agonists (IRAs), targeting either or both of the glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors, have proven to reverse BIR and improve cognition in mouse models of AD. We previously showed that many, but not all, IRAs can cross the blood-brain barrier (BBB) after intravenous (IV) delivery. Here we determined if widespread brain uptake of IRAs could be achieved by circumventing the BBB using intranasal (IN) delivery, which has the added advantage of minimizing adverse gastrointestinal effects of systemically delivered IRAs. Of the 5 radiolabeled IRAs tested (exenatide, dulaglutide, semaglutide, DA4-JC, and DA5-CH) in CD-1 mice, exenatide, dulaglutide, and DA4-JC were successfully distributed throughout the brain following IN delivery. We observed significant sex differences in uptake for DA4-JC. Dulaglutide and DA4-JC exhibited high uptake by the hippocampus and multiple neocortical areas. We further tested and found the presence of AD-associated Aβ pathology minimally affected uptake of dulaglutide and DA4-JC. Of the 5 tested IRAs, dulaglutide and DA4-JC are best capable of accessing brain regions most vulnerable in AD (neocortex and hippocampus) after IN administration. Future studies will need to be performed to determine if IN IRA delivery can reduce BIR in AD or animal models of that disorder [1)].

1)
Abdulhameed N, Babin A, Hansen K, Weaver R, Banks WA, Talbot K, Rhea EM. Comparing regional brain uptake of incretin receptor agonists after intranasal delivery in CD-1 mice and the APP/PS1 mouse model of Alzheimer's disease. Alzheimers Res Ther. 2024 Aug 1;16(1):173. doi: 10.1186/s13195-024-01537-1. PMID: 39085976.