Abstract

Alzheimer's disease (AD) and diabetes mellitus (DM) are both age related consequences occurred with loss of body efficiency to work properly and memorizing the daily tasks. Although lots of research efforts have been made to overcome these diseases, unfortunately all the drugs were failed to control and bounce back the person normal conditions. Recent research revealed a significant connection between metabolic impairment and these diseases involving insulin signaling and glucose regulation. Moreover due to impaired insulin signaling researchers thought AD as brain specific type-3 DM. Insulin receptors substrate proteins (IRSs) are involved insulin signaling and any impairment either genetic or post-translational modifications (PTMs) lead towards risk of AD and DM. Phosphorylation on tyrosine and serine/threonine residues are important PTMs that regulate IRSs functions and docking and un-docking of insulin with insulin receptors. Two types of IRSs i.e.1 and 2 are abundant in humans and are directly associated with insulin signaling, and improper dysfunction of both IRS-1 and 2 is thought as major step in progress of AD and DM. Interestingly, O-GlcNAc modification (addition of glucose molecule to serine or threonine residue) has inhibitory as well as dogmatic effects on IRSs functions. This cross-talk between these two PTMs regulates protein functions and working to get maximum output. Although a number of phosphorylated residues are confirmed experimentally on IRSs, however due to analytical difficulties experimental confirmation of exact O-GlcNAc modified residues is very difficult and time taking. In this study by using in-silico techniques we not only predict phosphorylation and O-GlcNAc residues on human IRS-1 and 2, but also calculate the 3D structure of these proteins to validate our predicted results. Both human IRS 1 and 2 have high potential of phosphorylation and O-GlcNAc modification not only on different serine and threonine residues but on same. These same residues are called as Yin-Yang sites and may be used as major therapeutic targets to overcome these diseases.