REVIEW ARTICLE

Insulin resistance in Alzheimer's disease

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The links between systemic insulin resistance (IR), brain-specific IR, and Alzheimer's disease (AD) has been an extremely productive area of current research. This review will cover the fundamentals and pathways leading to IR, its connection to AD via cellular mechanisms, the most prominent methods and models used to examine it, an introduction to the role of extracellular vesicles (EVs) as a source of biomarkers for IR and AD, and an overview of modern clinical studies on the subject. To provide additional context, we also present a novel analysis of the spatial correlation of gene expression in the brain with the aid of Allen Human Brain Atlas data. Ultimately, examining the relation between IR and AD can be seen as a means of advancing the understanding of both disease states, with IR being a promising target for therapeutic strategies in AD treatment. In conclusion, we highlight the therapeutic potential of targeting brain IR in AD and the main strategies to pursue this goal. (Translational Research 2016;■:1–15)

Abbreviations: AD = Alzheimer's disease; IR = insulin resistance

NORMAL INSULIN SIGNALING AND INSULIN RESISTANCE

Insulin is one of the key hormone regulators of metabolism throughout the body, through a variety of largely tissue-specific actions. Elevations in blood glucose and other nutrients after meals trigger the release of hormones which homeostatically regulate blood glucose levels, particularly insulin, which is secreted by the β cells of the pancreas,[1] and the insulin-regulating incretins, glucagon-like peptide-1 (GLP-1), and gastric inhibitory polypeptide. Insulin exerts its actions through binding of the extracellular α subunit of the insulin receptor, which leads to a conformational change that autophosphorylates the intracellular β subunit of the receptor via tyrosine kinase activation.[2] This kinase activation leads to the recruitment and phosphorylation of the insulin receptor substrates 1 and 2 (IRS-1 and IRS-2), which represent the first node in the insulin signaling cascade and exerts downstream effects on several key regulatory proteins of cell metabolism, cell survival, growth, and differentiation, including the mammalian target of rapamycin (mTOR), PKB, and glycogen synthase kinase 3 (GSK-3).[3,4] The divergent branches of the insulin pathway largely converge downstream onto Akt activation, primarily through PI3K activation of PDK.[5,6]

A key physiological action of insulin is to increase glucose uptake into cells, especially in muscle and adipose tissue,[1] by translocation of various insulin-dependent glucose transporters (GLUT) to the plasma membrane. Specifically, the insulin cascade leads to PI3K/PDK/Akt activation, which in turn leads to inactivation of AS-160,[7-9] which, coupled with the activation of other Rab GTPases, is thought to stimulate the translocation of certain insulin-dependent GLUTs, such as GLUT4, to the membrane.[10-12] Of particular interest for brain metabolism are GLUT1, GLUT4, and GLUT3. GLUT1 is present in nearly all cell types, whereas GLUT4 is primarily expressed in skeletal myocytes and adipocytes.[13-15] While GLUT3 is the primary brain neuronal GLUT and is mainly expressed in axons and dendrites, GLUT 1 and 4 have also been

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detected in brain tissue.[16,17] GLUT3 is unique in terms of its low Michaelis-Menten constant, allowing for continuous transport of glucose into neurons even under low extracellular concentrations thereby providing a consistent energy source.[18] Different isoforms of GLUT 1 mediate glucose uptake by astrocytes and the endothelial cells of the blood-brain barrier (BBB). The BBB contains insulin-independent GLUT1 and GLUT3 transporters that ensure a dynamic response of glucose transport to meet variable energy demands independent of insulin.[19] This dynamic responsiveness of the BBB is highlighted in a study that found that when glucose transport across the BBB was increased, the luminal expression of GLUT1 increased, whereas abluminal expression increased with decreased glucose transport.[20] On the other hand, BBB insulin receptor expression is reduced with prolonged peripheral hyperinsulinemia[21] and in aging,[22] whereas insulin levels in the brain of older individuals are also reduced.[23] The combined effects of aging and peripheral IR may lead to a substantial decrease in brain insulin and insulin receptors and a corresponding decrease in insulin-dependent glucose transport. The effects of decreased insulin signaling on glucose transport may also be differentially impacted on different brain regions depending on the type of GLUTs they express. GLUT4 mRNA colocalized with GLUT3, insulin, and insulin receptor mRNAs have been identified in the nuclei of basal forebrain cholinergic neurons, which may function as nutrient sensors. This partial GLUT4 dependence may help explain the vulnerability of these cells in low-energy conditions and Alzheimer's disease (AD).[18,24,25]

In insulin-resistant states such as type 2 diabetes mellitus (T2D), the ability of insulin to stimulate glucose uptake via insulin-dependent GLUT transporters is impaired, requiring higher than normal concentrations of extracellular insulin to maintain normal circulating glucose levels.[26] Early in the course of T2D, these higher insulin concentrations are maintained by β cell overstimulation.[27] Conditions of persistent insulin activation trigger the excessive autophosphorylation of various Ser/Thr residues on IRS family members.[28-30] This aberrantly phosphorylated IRS-1 has been implicated in several proposed mechanisms of insulin resistance (IR) based on different sites of hyperphosphorylation on Ser/Thr residues. In a feedforward loop, adaptive signaling elements such as mTORc and SK61 have been shown to hyperphosphorylate S632 and S302/S522 residues, respectively. This results in reduced insulin-binding sensitivity of the insulin receptor and subsequent cellular IR, as well as the translocation of the active portion of IRS from the membrane to the cytosol.[31-34] S337 phosphorylation on IRS-1 by GSK-3β has been shown to inhibit insulin signaling in humans,[35] whereas phosphorylation at S312 in humans stimulates uncoupling of IRS-1 and leads to its degradation.[36] Insufficient downstream signaling as a result of this degradation is another proposed hypothesis for IR.[37]

METHODS OF MEASURING INSULIN RESISTANCE

The gold standard for measuring whole-body IR is the euglycemic hyperinsulemic clamp technique. While this provides accurate and real-time data, the technique is laborious and invasive, requiring intravenous injection of insulin and glucose, as well as continuous blood collection over multiple hours.[38] The Oral Glucose Tolerance Test (OGTT) has long been used to quantify glucose intolerance, but by nature cannot serve as an indicator of IR. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), developed over 30 years ago by Matthews et al., provides an estimate of IR and β cell function by combining fasting insulin and glucose levels in a single metric.[39] Advances in computer-based modeling have led to the updated HOMA2-IR metric, improving reliability by accounting for various physiological adjustments. Nevertheless, it should be noted that transient fluctuations can also affect fasting glucose and insulin levels limiting the reliability of these metrics. The Somogyi effect, a somewhat rare phenomenon in T2D patients, results in hyperglycemia after extended hypoglycemia, particularly in the early morning. Coupled with the more common dawn effect, which results to variations in insulin levels due to circadian hormone fluctuations, it produces significant variability in fasting glucose and insulin levels. Because of these factors, it is imperative to develop rapid and reliable diagnostic markers for systemic and tissue-specific IR.

PERIPHERAL INSULIN RESISTANCE

Muscle. Chronic IR in skeletal muscle has long been considered a hallmark of T2D.[40] In an insulin-resistant state, muscle glycogen synthesis is impaired due to decreased glucose uptake.[41] This is thought to be the result of GLUT4 gene suppression due to excess free fatty acids.[42,43] Fatty acid levels have been shown to negatively correlate with insulin activity in skeletal muscle,[44] whereas high levels of saturated fatty acids can directly induce IR in skeletal muscle by inhibiting normal IRS-1 Tyr-phopshorylation.[45-48] Recent studies investigating O-linked-β-*N*-acetylglucosamine (O-GlcNAc) protein modifications have shown aberrant modification of IRS Ser/Thr residues (mediated by O-GlcNAc transferase [OGT] and β-N-acetylglucosaminidase [OGA]) interfering with IRS-PI3K interaction.[49,50]