Relationships Between Diabetes and Cognitive Impairment

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KEYWORDS

• Diabetes • Insulin resistance • Cognitive impairment • Neurodegeneration
• Alzheimer disease • Insulin sensitizers • Obesity

KEY POINTS

- Alzheimer disease is a neurodegenerative disease associated with impairments in glucose metabolism and insulin resistance in the brain.
- Many of the molecular and biochemical defects in Alzheimer disease are identical to those in either type 1 or type 2 diabetes mellitus as well as other insulin-resistance disease states.
- Peripheral insulin-resistance disease states, including diabetes, obesity, and nonalcoholic fatty liver disease, are associated with cognitive impairment and can exacerbate Alzheimer disease, (ie, cause it to progress).
- Therapeutic measures used for diabetes show efficacy in the early and moderate stages of Alzheimer disease.
- Endocrinologists and diabetologists should play a larger role in the early detection and monitoring of cognitive impairment in obese and/or diabetic patients.

INTRODUCTION

Like most organ systems throughout the body, the brain requires insulin and insulinlike growth factors (IGFs) to maintain energy metabolism, cell survival, and homeostasis. In addition, insulin and IGFs support neuronal plasticity and cholinergic functions, which are needed for learning, memory, and myelin maintenance. Impairments in insulin and IGF signaling, caused by receptor resistance or ligand deficiency, disrupt

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energy balance and disable networks that support a broad range of brain functions. Over the past several years, evidence that impairment in brain insulin and IGF signaling mediates cognitive impairment and neurodegeneration has grown, particularly in relation to mild cognitive impairment and Alzheimer disease (AD). Although amyloid deposits and phospho-tau–associated neuronal cytoskeletal lesions account for some AD-associated brain abnormalities, they do not explain the prominent and well-documented deficits in brain metabolism that begin very early in the course of the disease. Metabolic derangements in AD are similar to those in both type 1 type and 2 diabetes mellitus. However, the consequences of insulin/IGF receptor resistance and ligand deficiency include cognitive impairment and neurodegeneration caused by deficits in signaling through progrowth, proplasticity, and prosurvival pathways.

How brain insulin/IGF resistance and deficiency develop is not completely understood. Although a considerable number of studies have linked the recently increased rates of AD to other insulin resistance states, including obesity, type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease (NAFLD), and metabolic syndrome, it is important to realize that most cases of sporadic (nonfamilial) AD arise with no evidence of peripheral insulin-resistance disease. This review focuses on how peripheral insulin-resistance diseases, including diabetes mellitus, contribute to cognitive impairment and neurodegeneration. The working hypothesis is that peripheral insulin resistance promotes or exacerbates cognitive impairment and neurodegeneration by causing brain insulin resistance. Mechanistically, insulin resistance with dysregulated lipid metabolism leads to increased inflammation, cytotoxic lipid production, oxidative and endoplasmic reticulum (ER) stress, and worsening of insulin resistance. Some investigators are researching the role of cytotoxic ceramides that can promote inflammation, oxidative stress, and insulin resistance. Ceramides generated in liver or visceral fat can leak into peripheral blood because of local cellular injury or death, cross the blood-brain barrier, and initiate or propagate a cascade of neurodegeneration mediated by brain insulin resistance, inflammation, stress, and cell death (**Fig. 1**). These concepts help delineate the strategies needed to detect, monitor, treat, and prevent AD as well as other major insulin-resistance diseases.

INSULIN SIGNALING

The Master Hormone

Insulin is a 5800 Da, 51 amino acid polypeptide, composed of A (21 residues) and B (30 residues) chains linked by disulfide bonds. Banting, Best and others are credited for discovering insulin in pancreatic secretions,[1,2] and later it was shown that it reversed hyperglycemia.[3] Nearly 30 years later, methods to stabilize insulin, prolong its actions, and delay its absorption emerged; 50 years after its discovery, 99% pure insulin, free of proinsulin and other islet polypeptides, was produced.[4] Genetic engineering and yeast fermentation technology have enabled human insulin to be efficiently produced on a large scale.[5] The field continues to evolve, with some of the latest advances directed toward replacing injectable insulin with an oral form[6] and optimizing approaches for intranasal delivery of insulin to treat diabetes or cognitive impairment (see later discussion).[7–9]

Insulin-Stimulated Effects

The main targets of insulin stimulation include skeletal muscle, adipose tissue, and liver, although virtually all organs, tissues, and cell types are responsive to insulin. Insulin regulates glucose uptake and utilization by cells and free fatty acid levels in peripheral blood. Free fatty acids are substrates for generating complex lipids. In skeletal