Neurobiology of Disease 72 (2014) 92–103

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Review

Insulin resistance in Alzheimer's disease

Kelly T. Dineley [a], Jordan B. Jahrling [a,1], Larry Denner [b,*]

[a] Department of Neurology, University of Texas Medical Branch, Galveston, TX 77555, USA
[b] Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX 77555, USA

ARTICLE INFO

Article history:
Received 17 March 2014
Revised 2 September 2014
Accepted 5 September 2014
Available online 16 September 2014

Keywords:
Insulin resistance
Metabolism
Mitochondria
Alzheimer's disease
Animal models
Cognitive function
ERK
Learning and memory
Therapeutic windows
PPAR gamma

ABSTRACT

Insulin is a key hormone regulating metabolism. Insulin binding to cell surface insulin receptors engages many signaling intermediates operating in parallel and in series to control glucose, energy, and lipids while also regulating mitogenesis and development. Perturbations in the function of any of these intermediates, which occur in a variety of diseases, cause reduced sensitivity to insulin and insulin resistance with consequent metabolic dysfunction. Chronic inflammation ensues which exacerbates compromised metabolic homeostasis. Since insulin has a key role in learning and memory as well as directly regulating ERK, a kinase required for the type of learning and memory compromised in early Alzheimer's disease (AD), insulin resistance has been identified as a major risk factor for the onset of AD. Animal models of AD or insulin resistance or both demonstrate that AD pathology and impaired insulin signaling form a reciprocal relationship. Of note are human and animal model studies geared toward improving insulin resistance that have led to the identification of the nuclear receptor and transcription factor, peroxisome proliferator-activated receptor gamma (PPARγ) as an intervention tool for early AD. Strategic targeting of alternate nodes within the insulin signaling network has revealed disease-stage therapeutic windows in animal models that coalesce with previous and ongoing clinical trial approaches. Thus, exploiting the connection between insulin resistance and AD provides powerful opportunities to delineate therapeutic interventions that slow or block the pathogenesis of AD.

Contents

* Corresponding author at: Department of Internal Medicine, University of Texas Medical Branch, 301 University Blvd., Galveston, TX 77555-1060, USA.
E-mail address: ladenner@utmb.edu (L. Denner).
Available online on ScienceDirect (www.sciencedirect.com).
[1] Present address: Department of Physiology, University of Texas Health Science Center, San Antonio, TX 78229, USA.

http://dx.doi.org/10.1016/j.nbd.2014.09.001
0969-9961/

Introduction

Hippocampal functional and structural compromise is one of the earliest detectable traits of Alzheimer's disease (AD) (Boeve, 2012; Cavallucci et al., 2012) and is increasingly recognized as an important component of early AD pathology within the recently defined stages of early AD (Huijbers et al., 2014; Peters et al., 2014). The high glucose demand and insulin sensitivity of the hippocampus place it at particular risk for insulin resistance that is quintessential to aging and age-related disease states such as AD (Fehm et al., 2006). Given that the hippocampus is a vital integrator for new memory formation, applying our understanding of the molecular processes underlying hippocampal learning and memory (Sweatt, 2004; Xia and Storm, 2012) may facilitate the development of therapeutics with disease-modifying efficacy for early AD.

AD is characterized by age-dependent decline in cognition that, in its earliest stages, is the result of amyloid-β (Aβ)-mediated dysregulation of a variety of signaling cascades with ERK (extracellular signal-regulated kinase mitogen activated protein kinase) as a central integrator for hippocampal plasticity and memory. In this review, we focus on how insulin resistance may influence early AD cognitive impairment through the role of insulin signaling in hippocampal learning and memory (Fig. 1). This review will address the relationships between the insulin and ERK signaling cascades as they relate to learning and memory decline in early AD to explicate a new vision of disease progression and disease stage-specific therapeutic windows (Fig. 2).

Insulin signaling

Insulin is the predominant mediator of metabolic homeostasis by regulating glucose, energy, and lipids (Cheng et al., 2010; Shaham et al., 2008). After a meal, elevated glucose causes the pancreas to release insulin which stimulates muscle and adipocytes to take up glucose, thereby reducing plasma glucose. Insulin also regulates development, liver gluconeogenesis, fatty acid synthesis, and mitogenesis (Saltiel and Kahn, 2001; Taguchi and White, 2008). Insulin signals through its cell surface receptor tyrosine kinase that autophosphorylates and recruits adaptor proteins such as insulin receptor substrates 1 and 2 (IRS1, IRS2) (White, 2003) to initiate pleotropic actions through diverse signaling pathways with ERK serving as a prominent convergence point (Cheng et al., 2010). IRS activates phosphotidylinositide 3-kinase (PI3K) and PDK1 (phosphoinositide-dependent protein kinase-1) activation which then leads to Akt activation (Vadas et al., 2011). Akt is a central integrator of insulin signaling by sensing energy status, oxygen availability and growth factors to balance feeding-dependent lipogenesis with fasting-dependent gluconeogenesis through many signaling intermediates. For example, Akt drives GLUT (glucose transporter) plasma membrane translocation to normalize blood glucose and activates GSK-3β (glycogen synthase kinase-3β) to induce glycogen synthesis through the target of rapamycin complexes, including mTOR (mammalian target of rapamycin), to control AMPK, energy metabolism, mitochondrial function, synaptic plasticity and memory (Cheng et al.,

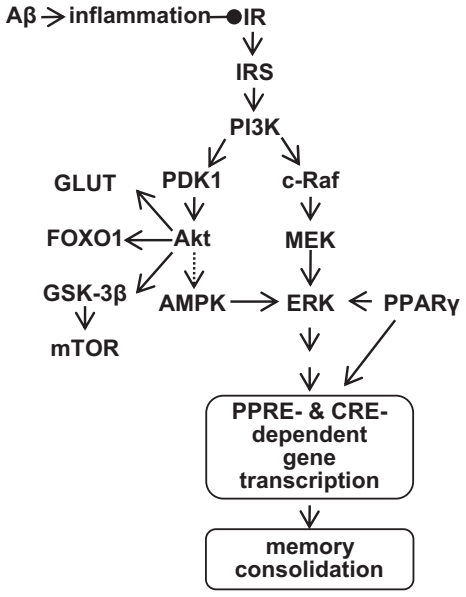

Fig. 1. Insulin signaling converges upon the ERK cascade. It is thought that Aβ-mediated neuroinflammation induces insulin resistance and hippocampal memory deficits since the insulin signaling axis couples to ERK. ERK is requisite for hippocampal memory consolidation and the insulin signaling axis converges on ERK via mediators of glucose utilization (GLUT, GSK-3β), mitochondrial function (FOXO1), and energy metabolism (mTOR, AMPK). Insulin sensitizers target PPARγ and AMPK to converge on ERK and memory consolidation through induction of CRE-containing genes. Many CRE-containing genes are also PPRE-containing genes indicating that PPARγ may also participate in gene transcription-dependent memory consolidation.

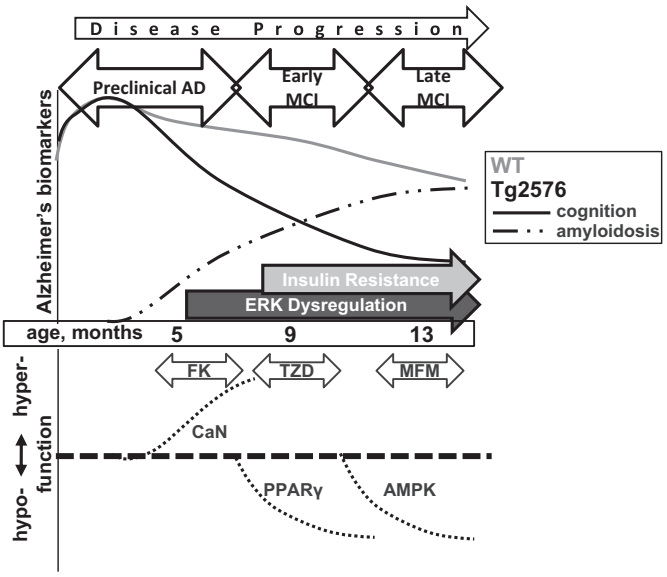

Fig. 2. Insulin resistance contributes to cognitive decline in Tg2576. Age-dependent exacerbation of insulin resistance manifested as sequential upregulation of calcineurin then downregulation of PPARγ (~9 MO) and AMPK (~13 MO) (lower panel dashed lines) suggest therapeutic windows for memory enhancement with mechanistically distinct insulin sensitizers to harness dysregulated ERK. While WT cognition declines slightly with age (solid gray line), by ~5 MO Tg2576 exhibit significant deficits in hippocampus-dependent memory that require proper ERK function (solid black line). Coincident are significant pathologies for amyloid and tau that continue to worsen with age (dashed black line). Therapeutic windows have been identified by which to enhance cognition by sequentially targeting calcineurin, PPARγ, and AMPK. FK = FK506.