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How does brain insulin resistance develop in Alzheimer's disease?

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Abstract Compelling preclinical and clinical evidence supports a pathophysiological connection between Alzheimer's disease (AD) and diabetes. Altered metabolism, inflammation, and insulin resistance are key pathological features of both diseases. For many years, it was generally considered that the brain was insensitive to insulin, but it is now accepted that this hormone has central neuromodulatory functions, including roles in learning and memory, that are impaired in AD. However, until recently, the molecular mechanisms accounting for brain insulin resistance in AD have remained elusive. Here, we review recent evidence that sheds light on how brain insulin dysfunction is initiated at a molecular level and why abnormal insulin signaling culminates in synaptic failure and memory decline. We also discuss the cellular basis underlying the beneficial effects of stimulation of brain insulin signaling on cognition. Discoveries summarized here provide pathophysiological background for identification of novel molecular targets and for development of alternative therapeutic approaches in AD.

Keywords: Alzheimer's disease; Amyloid-β oligomers; Insulin resistance; Insulin therapy; GLP-1R agonists

1. Introduction

Understanding the molecular basis of neuronal dysfunction and memory loss in Alzheimer's disease (AD) has become a major research and public health challenge because the number of cases is predicted to increase exponentially during the next few decades, and effective treatments capable of halting disease progression are still lacking [1,2]. With only a small subset of cases attributed to inherited genetic causes [3], the mechanisms of pathogenesis and etiology of sporadic, late-onset AD are still not elucidated fully. Thus, identification of molecular components and pathways that contribute to this complex neurological disorder has been the focus of intense research efforts during the past few years.

Recent evidence indicates that AD is a brain-specific form of diabetes [4,5]. The intriguing connection between diabetes and AD was identified initially in the Rotterdam study, which revealed that diabetes increases the risk of dementia [6,7]. Subsequent clinical and epidemiologic studies have confirmed this association (reviewed in [8]) and demonstrated that impaired metabolic parameters, such as hyperglycemia and hyperinsulinemia, correlated positively with development of AD-related pathology in humans [9–11]. Moreover, AD brains exhibit defective insulin signaling, altered levels and/or aberrant activation of components of the insulin signaling pathway, and, more importantly, decreased responsiveness to insulin [12–14].

In peripheral tissues (e.g., liver and muscle), insulin signaling stimulates glucose uptake and promotes metabolic reprogramming after feeding [15]. Although the brain was once considered an insulin-insensitive organ, and the source of brain-acting insulin is still a matter of debate [16], it is now established that insulin actions are important for neuronal survival and brain function [17]. Although at that time broader roles of brain insulin signaling were still unknown, early studies demonstrated that insulin regulates brain metabolism and body energy balance by acting on the hypothalamus [18]. In addition to its role in hypothalamic metabolic control, insulin signaling has now been shown to play important roles in other brain regions. Insulin receptors and downstream

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components of canonical insulin signaling are present and active in various forebrain areas important for memory formation, consolidation, and retrieval [19], including the hippocampus [17]. Insulin actions were shown recently to be required for synaptic plasticity, learning, and memory [17,20–22]. Furthermore, in vitro and in vivo evidence supports the notion that insulin has neuroprotective [23,24] and memory-enhancing properties [25,26], indicating a permissive role for insulin in cognition [27]. Thus, it is likely that defects in brain insulin signaling may give rise to neuronal dysfunction and cognitive deficits that are characteristic of AD.

Our understanding of the molecular underpinnings of why AD is a memory disorder has increased significantly during the past 15 years. For decades, it was thought that neuritic or senile plaques, neuropathological hallmarks of AD mainly composed of large aggregates and amyloid fibrils of the amyloid-β (Aβ) peptide, triggered neuronal death and caused memory impairment in patients with AD [28]. However, despite the demonstrated in vitro neurotoxicity of Aβ fibrils, a puzzling observation resulting from careful neuropathological examination of post mortem AD brains was that amyloid burden did not correlate well with premortem cognitive decline [29,30]. Instead, those studies showed that cognitive deficits were highly correlated with synapse loss [30–32], and suggested that an as-yet-unidentified toxin, but not amyloid plaques, was responsible for triggering memory loss in AD. Identification of soluble amyloid-β oligomers (AβOs) as synaptotoxins that accumulate in AD brains [33–36] stimulated a paradigm shift in the field, with AβOs now considered the proximal toxins responsible for synapse dysfunction and memory failure in AD (for recent reviews, see [1,37–39]).

In the following sections, we review recent findings linking the neurotoxic impact of AβOs and defects in brain insulin signaling in AD. Because these data indicate a close similarity between pathways that drive peripheral insulin resistance in diabetes and brain insulin dysfunction in AD, we summarize further and discuss the molecular bases for using antidiabetic agents as novel therapeutic approaches in AD.

2. Deregulated brain insulin signaling in AD

In peripheral metabolic disorders, such as type 2 diabetes, prolonged metabolic stress and proinflammatory signaling lead to attenuated insulin signaling and decreased cellular responsiveness to insulin [40]. This pathological state is referred to as insulin resistance and it impairs acutely the ability of cells to maintain energy homeostasis. Interestingly, AD brains present similar abnormalities, including metabolic stress and neuroinflammation [12–14,41–43]. Thus, it is conceivable that similar mechanisms account for peripheral insulin resistance in type 2 diabetes and impaired brain insulin signaling in AD. Indeed, recent studies have linked neuropathogenic mechanisms triggered by AβOs to mechanisms involved in peripheral insulin resistance in diabetes [41,44,45].

Physiologically, insulin binds to its cell surface receptor (insulin receptor [IR]) and triggers intrinsic IR tyrosine kinase activity. Activated IRs then phosphorylate members of a conserved family of adaptor proteins called insulin receptor substrates 1 through 4 (IRS-1 through IRS-4) [15]. Once phosphorylated at tyrosine residues, IRS proteins act as scaffolds that couple IR stimulation to downstream effectors, such as phosphoinositide 3-kinase (PI3K), murine thymoma viral oncogene homolog (or Akt)/protein kinase B, and mammalian target of rapamycin complex 1 [15], allowing metabolic and transcriptional reprogramming of cells [46]. On the other hand, IRS-1 and IRS-2, the best-studied components of the IRS family, can undergo inhibitory serine phosphorylation (pSer), which causes their dissociation from the IR and decreases tyrosine phosphorylation (pTyr) [46]. Therefore, an intricate balance between IRS phosphorylation at serine or tyrosine residues (IRS-1pSer vs. IRS-1pTyr) determines the extent of insulin actions [47].

In type 2 diabetes, aberrant tumor necrosis factor-α (TNF-α) signaling leads to activation of the stress kinase c-Jun N-terminal kinase (JNK) [48]. Activated JNK phosphorylates IRS-1 at serine residues (IRS-1pSer), blocking downstream insulin signaling and causing peripheral insulin resistance [40]. Similarly, it was shown recently that AβOs instigate aberrant activation of the TNF-α/JNK pathway and IRS-1 inhibition in primary hippocampal neurons [41,44], and in the hippocampi of cynomolgus monkeys that received intracerebroventricular infusions of AβOs [41]. IRS-1 inhibition was also demonstrated in the brains of a transgenic mouse model of AD [41]. Most important in establishing the clinical relevance of these findings was the demonstration of elevated IRS-1pSer [14,41] and activated JNK [41] in postmortem AD brains. Because AβOs trigger internalization and redistribution of neuronal IRs [49], it is possible that removal of IRs from the cell surface facilitates IRS-1pSer, a view that is consistent with our finding that insulin blocks both neuronal IR downregulation [50] and IRS-1pSer induced by AβOs [41].

Downstream from IRS-1 and PI3K, AβOs instigate Ser473 phosphorylation of Akt, a molecular hub in the insulin signaling pathway. Elevated pSer473 levels are associated with feedback-dependent Akt inhibition in inflammation and peripheral insulin resistance [51,52]. Interestingly, induction of Akt-pSer473 by AβOs takes place both in the absence and presence of insulin [49], suggesting that it could be mediated by an IR-independent pathway, likely involving TNF-α signaling.

In peripheral insulin resistance, activation of the TNF-α/JNK pathway is linked to major inflammatory/stress signaling networks, including endoplasmic reticulum (ER) stress and the stress kinases IκBα kinase (IKK) and double-stranded RNA-dependent protein kinase (PKR) [53,54]. We recently reported that IκBα kinase and double-stranded RNA-dependent protein kinase appear to mediate AβO-induced IRS-1 inhibition in hippocampal neurons [41]. It is also conceivable that ER stress, which has been reported in AD brains [43,55], further underlies oligomer-induced