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Insulin Signaling in Sporadic Alzheimer's Disease

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Abstract

Excessive production of β -amyloid (A β) peptides from proteolytic cleavage of amyloid precursor protein is believed to play a central role in the pathogenesis of Alzheimer's disease (AD). In particular, accumulated intracellular A β is found in vulnerable neurons, and the soluble oligomers of A β peptides [also termed A β -derived diffusible ligands (ADDLs)] are highly toxic to neurons. Evidence shows that both extracellular and intracellular ADDLs can compromise insulin signaling. Extracellular ADDLs can bind to synapses and decrease membrane insulin receptors (IRs) through an insulin signaling-dependent mechanism. Intracellular A β inhibits IR signaling in neurons by interfering with the association between phosphoinositide-dependent kinase 1 and Akt1 to preclude Akt1 activation. Together, these findings suggest that agents that stimulate insulin signaling may have neuroprotective effects. Indeed, insulin and insulin sensitizers have been shown to improve cognitive and memory functions in animal models of AD, as well as in AD patients.

Alzheimer's disease (AD) is a devastating neurodegenerative disorder that causes memory loss initially, followed by dementia, with age, genetic, and environmental factors contributing to its development and progression (1). It is widely accepted that excessive production of β -amyloid (A β) peptides from the proteolytic cleavage of amyloid precursor protein (APP) plays a central role in AD pathogenesis (2). Soluble oligomers of A β peptides, also termed A β -derived diffusible ligands (ADDLs), are highly toxic to neuronal cultures and cause AD-like memory loss in animals based on various spatial learning and memory tests (3–5). Furthermore, accumulation of intracellular A β is found in vulnerable neurons in AD brains, which appears to be an early event associated with synaptic dysfunction in several AD mouse models (6, 7). On the other hand, epidemiological, clinical, and experimental evidence suggest a link between AD and insulin resistance (8–13). AD is also termed “type 3 diabetes” because normal amounts of insulin are inadequate to produce a normal insulin response in the brain. In addition, concentrations of insulin and insulin-like growth factors (IGFs), as well as their receptor-mediated signaling, are markedly reduced (14, 15). However, how ADDLs and intracellular A β cause insulin resistance in the central

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nervous system has remained a fundamental, unanswered question. Two papers now shed light on the interplay between A β or ADDLs and insulin signaling and resistance.

Extracellular ADDLs

Proper insulin signaling is crucial for synaptic plasticity by promoting both excitatory glutamatergic and inhibitory GABAergic transmissions (16, 17). ADDLs impair long-term potentiation, a paradigm of cognitive and memory function (18). Also, soluble A β oligomers inhibit insulin signaling (19). De Felice and collaborators (20) showed that ADDLs bound to synaptic sites on the dendrites of cultured hippocampal neurons, causing neuronal oxidative stress, removal of insulin receptors (IRs) from dendritic plasma membranes, and loss of synapses. Insulin prevented these effects. Moreover, rosiglitazone, an insulin-sensitizing drug used to ameliorate insulin resistance in type 2 diabetes patients, enhanced the protective effects of insulin. What could constitute the mechanism of this protective effect? The molecular identity of the synaptic binding sites for ADDLs remains to be determined. However, ADDLs did not bind directly to IRs and did not compete with insulin for binding to IRs. Moreover, insulin failed to block ADDL binding in the presence of the IR tyrosine kinase inhibitor AG1024, indicating an insulin signaling-dependent effect. It is possible that ADDLs not only cause IR internalization but also modulate other membrane proteins, including receptors such as N-methyl-D-aspartate (NMDA) receptors, by reducing their cell surface density (21, 22). Therefore, it is plausible that ADDLs interact with specific membrane-bound protein complexes that contain these receptors, which are then internalized by an unknown mechanism. Although there is much controversy in the field regarding whether A β needs a specific membrane receptor to exert neurotoxicity, the findings of De Felice et al. (20) indicate that it requires specific membrane protein components as well as IR-mediated intracellular signaling events, a notion that was affirmed by the neuroprotective effect of the insulin-sensitizing drug rosiglitazone.

Two major conclusions can be drawn from this work. First, the early neuronal damage in AD that is caused by ADDLs may be triggered, at least in part, by ADDL-mediated IR internalization and a concomitant decrease in insulin signaling (Fig. 1). Second, stimulation of insulin signaling may be a potential neuroprotective strategy that could be used as an AD therapy. Two major conclusions can be drawn from this work. First, the early neuronal damage in AD that is caused by ADDLs may be triggered, at least in part, by ADDL-mediated IR internalization and a concomitant decrease in insulin signaling (Fig. 1). Second, stimulation of insulin signaling may be a potential neuroprotective strategy that could be used as an AD therapy.

Intracellular A β

The Akt pathway shapes cellular responses to trophic factors, metabolic signals, and environmental stress, and regulates homeostatic functions such as survival, growth, and differentiation (23). Stimulated insulin- and IGF-receptor tyrosine kinases phosphorylate the insulin receptor substrate (IRS), an adaptor that activates phosphoinositide 3-kinase (PI3K), which consists of the p85 and p110 subunits and catalyzes the 3'-phosphorylation of inositol lipids, such as phosphatidylinositol 3,4,5-trisphosphate (PIP₃). PIP₃ recruits

phosphoinositide-dependent kinase (PDK) and the serine-threonine kinase Akt to the plasma membrane through its interactions with the pleckstrin homology (PH) domains of these kinases, resulting in Akt activation after two sequential phosphorylations at Thr³⁰⁸ and Thr⁴⁷³ by a PI3K-dependent mechanism (24).

Lee and collaborators (25) sought to identify the molecular components of the insulin signaling pathway that are targeted by intraneuronal A β . Akt phosphorylation and activity were reduced in extracts of AD brain tissue compared to controls. Likewise, insulin stimulation of cultured neuroblastoma cells overexpressing intracellular A β reduced the abundance of total and phosphorylated Akt compared to untreated controls. A potential mechanism of action was suggested: ADDLs impaired the interaction between purified PDK and Akt in an in vitro system, and the association of PDK and Akt (as shown by coimmunoprecipitation) was reduced in the brain tissue of AD patients. The authors proposed that intracellular A β in neurons inhibits IR signaling by interfering with the association between PDK and Akt1, precluding Akt1 activation and eliminating the neuroprotective benefit of insulin (Fig. 1). Intraneuronal A β had no effect on the enzymatic activities of Akt and other signaling components when added under conditions in which the enzymes were already in their active states.

Intracellular or Extracellular?

The two papers discussed here independently point to the importance of insulin signaling in suppressing molecular events that are relevant to the development of AD. They also suggest that insulin signaling may have neuroprotective effects in patients with AD. The results, however, differ in other important aspects. The two papers present very different targets for A β and ADDLs, one being an extracellular ADDL binding site on neuronal dendrites, and the other an intracellular interaction between PDK and Akt. It is possible that both scenarios are compatible with biological reality: Both targets could be relevant to AD and A β , and ADDLs could act both extracellularly and intracellularly to impair insulin signaling. It is not clear which source of A β or ADDLs plays the pivotal role. Amyloid peptides are generated intracellularly (2), but they can also be taken up into cells from an extracellular source (26). However, intracellular A β has been increasingly considered an early marker of AD neuropathology (3, 4). Furthermore, APP processing and A β metabolism are regulated by insulin, IGF-1, and their signaling pathways. Insulin degrading enzyme (IDE) is the major protease that degrades A β in the brain (27), and insulin treatment or activation of its downstream signaling pathway reduces intracellular A β amounts and increases A β secretion by increasing competition between insulin and A β for IDE (27). Thus, we speculate that intracellular A β is more likely to be the key target of the insulin-mediated protective effect. This is supported by recent animal data showing that targeting intracellular A β by a specific γ -secretase inhibitor or by immunotherapy at an early stage of the disease can prevent synaptic dysfunction in mouse models of AD (8).

Clinical Implications

The cell-protective effects of Akt signaling have been previously recognized (such as in cancer), and the neuroprotective actions of growth factors that signal through Akt are also

well known. However, the concept of insulin signaling in the brain in the context of neuroprotection in AD is unexpected. To date, there is no effective therapy for AD, and therapies currently in use do not prevent or reverse the disease. A wide variety of therapeutic approaches are under clinical investigation, many of which focus on targeting A β , although others seek to exploit different neuroprotective approaches. Among them, two approaches that involve enhancement of insulin signaling are of particular interest. Clinical trials using the insulin-sensitizing peroxisome proliferator-activated receptor γ (PPAR γ) agonist rosiglitazone and an intranasal insulin therapy have yielded encouraging results in terms of improving cognition in patients at an early stage of AD (28–30). Thus, the two papers discussed here provide a potential scientific basis for these clinical results.

In conclusion, we point out that the pursuit of insulin signaling-based AD therapies may have far-reaching consequences. For example, various other trophic factors, such as IGFs, fibroblast growth factors (FGFs), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and soluble APP, have neuroprotective activities that depend on Akt activation, perhaps even more so than insulin. Will success with insulin encourage preclinical and clinical work with other Akt-activating agents? Furthermore, current efforts with rosiglitazone and other insulin-sensitizing agents in AD therapy, which owe their scientific rationale to what has been learned about type 2 diabetes, have yielded promising results. Indeed, the term “type 3 diabetes” has already been coined for insulin resistance associated with AD (14, 15, 31). If the concept holds up to reality, what may ultimately emerge are entirely different therapies for AD.

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Fig. 1.

The effects of A β on insulin signaling in neurons. Lee et al. posit that intracellular A β in neurons interferes with the interaction between PDK and Akt (25). This is supported by findings of lowered Akt activity in AD brain tissue and in insulin-treated cells overexpressing A β , as well as an observed decrease in coimmunoprecipitation. De Felice et al. suggest that extracellular ADDLs bind at specific synaptic sites on neuron dendrites (20), causing oxidative stress and decreasing the abundance of cell surface insulin receptors through internalization. ADDLs do not bind directly to the IRs and do not compete with insulin for receptor binding. ADDLs may bind with low affinity to protein complexes containing NMDA receptors, leading to internalization through an unknown mechanism. pY, phosphotyrosine.