Neuropharmacology 136 (2018) 192–195

Contents lists available at ScienceDirect

Neuropharmacology

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

Invited review

Reduced brain insulin signaling: A seminal process in Alzheimer's disease pathogenesis

George S. Bloom [a, b, c, *], John S. Lazo [d, e], Andrés Norambuena [a]

[a] Department of Biology, University of Virginia, Charlottesville, VA, USA
[b] Department of Cell Biology, University of Virginia, Charlottesville, VA, USA
[c] Department of Neuroscience, University of Virginia, Charlottesville, VA, USA
[d] Department of Pharmacology, University of Virginia, Charlottesville, VA, USA
[e] Department of Chemistry, University of Virginia, Charlottesville, VA, USA

ARTICLE INFO

Article history:
Received 5 July 2017
Received in revised form
8 September 2017
Accepted 10 September 2017
Available online 29 September 2017

Keywords:
Alzheimer's disease
Insulin
Amyloid-β
Tau
mTOR

ABSTRACT

The synaptic dysfunction and death of neurons that mediate memory and cognition account together for the behavioral symptoms of Alzheimer's disease (AD). Reduced insulin signaling in the brain is a hallmark of AD patients, even in the absence of systemic type 1 or type 2 diabetes, prompting some researchers to refer to AD as brain-specific, or type 3 diabetes. A key question that arises about this signature feature of AD is "how, if at all, does the brain's impaired ability to utilize insulin contribute to the behavioral deficits associated with AD?" The fact that type 2 diabetes is a risk factor for AD suggests a causative role for impaired insulin responsiveness in AD pathogenesis, but how that might occur at a detailed molecular level had been elusive. Here we review recent findings that mechanistically link soluble forms of amyloid-β (Aβ) and tau, the respective building blocks of the amyloid plaques and neurofibrillary tangles that accumulate in the brains of AD patients, with neuronal decline that is associated with poor insulin responsiveness and may begin long before AD symptoms become evident. We discuss how Aβ and tau work coordinately to deprive neurons of functionally accessible insulin receptors and dysregulate normal signaling by the protein kinase, mTOR. Finally, we suggest how newly gained knowledge about pathogenic signaling caused by reduced brain insulin signaling might be exploited for improved early detection and therapeutic intervention for AD.

This article is part of the Special Issue entitled 'Metabolic Impairment as Risk Factors for Neurodegenerative Disorders.'

© 2017 Elsevier Ltd. All rights reserved.

Contents

1. Introduction

The defining features of Alzheimer's disease (AD) are memory and cognitive deficits, and the accumulation in brain of two types of abnormal, poorly soluble structures, amyloid plaques made from

Abbreviations: Aβ, amyloid-β; AβO, amyloid-β oligomer; AD, Alzheimer's disease; CCR, cell cycle re-entry; IR, insulin receptor; JNK, c-Jun *N*-terminal kinase.

* Corresponding author. University of Virginia, Department of Biology, PO Box 400328, Charlottesville, VA, 22904-4328, USA.
E-mail address: gsb4g@virginia.edu (G.S. Bloom).

https://doi.org/10.1016/j.neuropharm.2017.09.016
0028-3908/© 2017 Elsevier Ltd. All rights reserved.

amyloid-β (Aβ) peptides and neurofibrillary tangles made from the neuron-enriched, microtubule-associated protein, tau. The behavioral deficits associated with AD are caused by synaptic dysfunction of neurons that mediate memory and cognition, and by the death of those neurons. This demise of neuron function and viability are mediated in turn by biochemical and cell biological connections between Aβ and tau, especially soluble forms that represent building blocks of plaques and tangles (Bloom, 2014).

Among the lesser known characteristics of AD are impaired brain insulin signaling and re-entry into the cell cycle of differentiated neurons that normally would be in a permanent post-mitotic state. Remarkably, insulin resistance can occur independently of systemic type 1 or type 2 diabetes, prompting the idea that AD represents a brain-specific, or type 3 diabetes (de la Monte, 2014; Steen et al., 2005). Besides the obvious metabolic implications, mechanistic connections between poor insulin signaling in brain and specific AD phenotypes had been shrouded in mystery until recently. Ironically, there is no evidence to indicate that ectopic neuronal cell cycle re-entry (CCR) culminates in cell division to create new neurons. Instead, CCR apparently is a prelude to neuron death and may account for up to 90% of the neuron loss in AD (Arendt et al., 2010).

Brain insulin resistance could represent a lesion that is far upstream in the web of events that culminates in AD, or alternatively, it could arise downstream of signaling processes that have already compromised synaptic function or placed neurons on a death pathway. The fact that type 2 diabetes is a risk factor for AD (Craft, 2007) implies that brain insulin resistance is a causative factor for AD, but does not reveal any mechanistic details for why that is so. In this review, we focus on recent studies that, taken together, connect the dots represented by Aβ, tau, reduced brain insulin signaling and neuronal CCR into a picture that places neuronal insulin resistance at a seminal stage of AD pathogenesis.

2. How brain-specific insulin resistance is induced acutely

One of the first clues to how neurons become insulin insensitive was provided when Aβ oligomers (AβOs) were found to provoke rapid and extensive redistribution of insulin receptors (IRs) from the cell surface of cultured neuron dendrites into the somatic cytoplasm by a mechanism that involves calcium entry into dendrites via NMDA receptors (Zhao et al., 2008). Considering that this effect is robust within 30 min of neuronal exposure to AβOs, it likely occurs independently of protein synthesis and degradation, but instead probably reflects a net increase in the ratio of IR endocytosis to exocytosis. Although the mechanism that drives this apparent alteration in IR trafficking remains unknown, the functional consequence is that IRs are sequestered from the extracellular space, and are thereby inaccessible to the ligands they must bind to initiate insulin signaling.

IR sequestration is not the only mechanism by which AβOs reduce neuronal insulin signaling. AβOs also induce secretion of TNFα in primary neuron-containing cultures, and binding of the TNFα to neuronal TNFα receptors leads to stimulation of c-Jun *N*-terminal kinase (JNK) signaling (Bomfim et al., 2012). A major substrate of JNK is insulin receptor kinase substrate-1 (IRS-1), whose JNK-stimulated phosphorylation suppresses insulin signaling by preventing activation of two protein kinases, PI3 kinase and Akt, that would otherwise enable insulin action further downstream (Ozes et al., 2001).

One source of the TNFα that drives this process is microglia. Although neurons are the best known direct cellular targets of AβOs, microglia are also affected by these small Aβ complexes. Exposure of primary microglia to AβOs was found to induce secretion of TNFα, which in turn was able to drive JNK activation in primary neurons (Bhaskar et al., 2014). Because microglia are common constituents of primary neuron cultures, it is likely that at least some of the impaired neuronal insulin signaling caused by exposing primary neurons to AβOs was triggered by microglial-derived TNFα. Astrocytes are also abundant in primary neuron cultures and are another probable source of TNFα in AβO-treated cultures (Carrero et al., 2012).

As shown in Fig. 1, AβOs thus appear to reduce neuronal insulin signaling acutely by two mechanisms: internalization of IRs and TNFα-induced interference with the insulin signaling pathway beyond IRS-1. AβO-stimulated microglia and astrocytes supply at least some of the TNFα, which acts on neurons following engagement with neuronal TNFα receptors. It is not yet known if secreted TNFα mediates IR sequestration in addition to its role in blocking insulin signaling beyond IRS-1.

The results just described refer to carefully controlled experiments in which soluble AβOs were abruptly applied to primary mixed cultures of neurons and glia, and to neuronal responses that depended on soluble, endogenous tau. Although such precipitous increases in extracellular AβOs are unlikely to occur *in vivo*, a slow, but steady buildup of AβOs over many years may provoke similar effects during pre-symptomatic AD stages. Indeed, there is now provocative, but compelling evidence that the biochemical and cell biological processes that lead to full blown AD begin more than 20 years before symptoms become evident (Shaw et al., 2007; Villemagne et al., 2013).

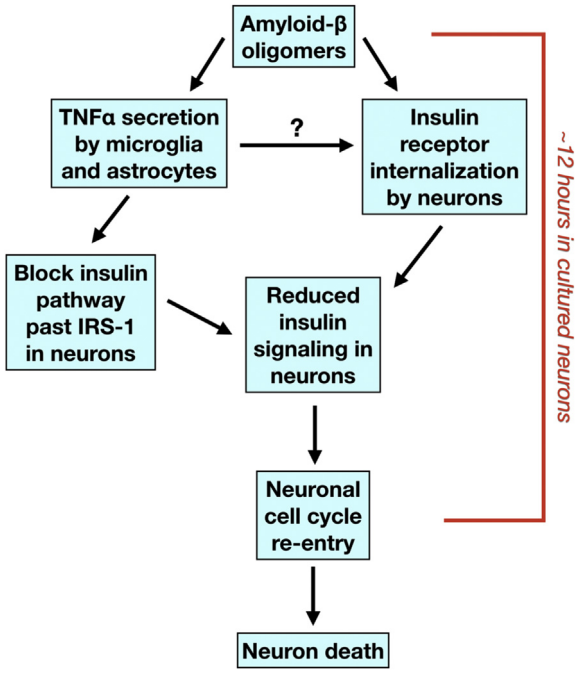

Fig. 1. Acute neuronal insulin resistance induced by amyloid-β oligomers. The oligomers cause reduced insulin signaling in neurons by at least two pathways. They induce microglia and astrocytes to secrete TNFα, which blocks insulin signaling past IRS-1 in neurons following binding to neuronal TNFα receptors. In addition, amyloid-β oligomers cause a rapid, extensive internalization of insulin receptors, a process that may or may not depend on the secreted TNFα. The reduced insulin signaling is a direct cause of neurons ectopically re-entering the cell cycle, which ironically leads to their eventual death, instead of their replication. Re-entry of neurons into the cell cycle is evident within ~12 h of their initial exposure to amyloid-β oligomers, is tau-dependent, and occurs independently of the respective incorporation of amyloid-β and tau into plaques and tangles. Overall, this process emphasizes that the ability of amyloid-β oligomers to cause neuronal insulin resistance unleashes their further toxic potential to drive neurons back into the cell cycle, a prelude to neuron death in AD.

3. Chronic IR reduction in AD

To assess whether chronic exposure of neurons to AβOs *in vivo* affect insulin signaling by additional mechanisms, quantitative RT-PCR and western blotting have been used to measure IR mRNA and protein in human brain tissue samples. This approach demonstrated an ~15-fold drop in IR mRNA in the hippocampus for AD patients compared to age-matched, cognitively normal controls (Steen et al., 2005). Although up to 2/3 of hippocampal CA1 neurons may eventually die in AD (West et al., 1994), the loss of such neurons could account for only a minor fraction of the reduced IR mRNA in the AD hippocampus. The bulk of the IR mRNA loss in the AD hippocampus must therefore be explained by a reduced steady state level of cellular expression.

Paralleling the reduction of IR mRNA in AD is a corresponding, though less extreme loss of IR protein. Comparison of AD versus control brain for IR protein levels by western blotting revealed an ~50% reduction in AD (Steen et al., 2005). When the evidence cited here is considered collectively, neuronal insulin resistance in AD appears to involve an acute stage, in which AβOs cause sequestration of IRs away from the plasma membrane and separately interfere with signaling initiated by IRs, and a chronic phase, in which levels of IR mRNA and protein are reduced by as yet undetermined mechanisms.

4. How reduced insulin signaling adversely affects neurons

By 2005, a body of evidence that had been accumulating since the 1990's prompted the suggestion that AD should be regarded as brain-specific, or type 3 diabetes (Steen et al., 2005). Most such evidence concerned deficient glucose utilization beginning at early disease stages, and as just described, reduced levels of IR mRNA and protein in AD brain. How those defects might relate mechanistically to the synaptic dysfunction and neuron death that together underlie the behavioral symptoms of AD, though, remained poorly understood until recently.

That veil of mystery has now been partially lifted through studies of neuronal CCR, which has been estimated to account for up to 90% of neuron death in AD (Arendt et al., 2010). Building on work from others who showed that AD-like CCR can be recapitulated in cultured rodent neurons by exposing them to oligomeric, but neither monomeric nor fibrillar Aβ (Varvel et al., 2008), we discovered that CCR depends on site-specific tau phosphorylation catalyzed by multiple protein kinases activated by AβOs (Seward et al., 2013). The kinases in question include fyn, PKA and CaMKII, which respectively must phosphorylate tau at Y18, S409 and S416 for CCR to occur (note: these sites refer to the longest isoform, 2N4R, of human CNS tau). Interestingly, microglial-derived TNFα was also found to induce CCR of primary neurons (Bhaskar et al., 2014), indicating that this inflammatory cytokine transduces signals from AβOs to neuronal TNFα receptors not only to suppress insulin signaling (Bomfim et al., 2012), but to activate the cell cycle machinery as well.

In a subsequent study, we found a fourth site on tau, S262, that must also be phosphorylated to enable CCR, and that S262 phosphorylation depends on AβO-stimulated activation of mTOR, a serine-threonine protein kinase (Norambuena et al., 2017). Functional forms of mTOR are incorporated into either of two membrane-associated, multi-protein complexes, mTORC1 and mTORC2, that collectively guide cellular behavior in response to extracellular clues, like insulin, growth factors and nutrients, such as amino acids and glucose (Zoncu et al., 2011). One common consequence of mTORC1 activation is progression through the cell cycle (Zoncu et al., 2011).

Using cultured mouse neurons and transgenic mice, we found that both mTORC1 and mTORC2 must be activated by AβOs for CCR to proceed, and that tau phosphorylation at S262 requires mTORC1 activation (Norambuena et al., 2017). Activation of mTORC1 by AβOs was found to be unconventional. Whereas other known stimulators of mTORC1 activate the complex at the lysosomal surface, which leads to autophagy suppression (Zoncu et al., 2011), AβOs activate mTORC1 at the plasma membrane instead. Remarkably, this mislocalized mTORC1 activation depends not only on the presence of tau, but on its mTORC1-dependent phosphorylation at S262, as well (Norambuena et al., 2017). AβOs therefore induce a toxic feedback loop between tau and mTORC1, whereby the latter must induce tau phosphorylation at S262 so the former can accumulate at the plasma membrane, instead of at lysosomes. Tau phosphorylation at that site probably is not catalyzed directly by mTORC1, but instead by S6K, which is phospho-activated by mTORC1 (Brown et al., 1995) and is known to phosphorylate tau at S262 (Pei et al., 2008). Finally, we found that CCR can be blocked by stimulating lysosomal mTORC1 by any of several experimental manipulations while mTORC1 is activated simultaneously at the plasma membrane by AβOs. One such experimental manipulation is the simple addition of insulin to the culture medium (Norambuena et al., 2017).

Taken together, our work on AβO-induced neuronal CCR (Norambuena et al., 2017; Seward et al., 2013) and the work of others on AβO-induced insulin resistance (Bomfim et al., 2012; Zhao et al., 2008) implies that the ability of AβOs to inhibit neuronal responses to insulin unleashes their further toxic potential to cause CCR, and by extension, neuron death. It is also important to note that CCR can be detected within hours of neuronal exposure to AβOs, indicating that this phenomenon represents a seminal process in AD pathogenesis and may be occurring neuron-by-neuron over the course of many years in pre-symptomatic stages of AD. Moreover, although neuronal CCR is initiated by Aβ and proceeds by a tau-dependent mechanism, it occurs independently of the respective incorporation of Aβ and tau into plaques and tangles.

5. Clinical implications

The evidence reviewed here that insulin resistance is a prime factor in early AD pathogenesis suggests insulin administration as a potential disease-modifying therapy, with some important caveats. The two most obvious caveats of such an approach are the risk of systemic hypoglycemia and the fact that the brain's capacity to utilize insulin is hampered by downstream effects of AβO accumulation in brain, most notably IR sequestration and interference with the neuronal insulin signaling pathway past IRS-1 (see Fig. 1). While there is no reason to expect that insulin therapy would reduce the Aβ burden in brain, delivering sufficiently concentrated insulin directly to brain regions affected in AD might support enough neuronal insulin signaling to suppress CCR and subsequent neuron death. Considering evidence that insulin protects cultured neurons from AβO-induced synapse loss (De Felice et al., 2009), insulin administration *in vivo* might also provide the AD brain with at least some protection against further synaptic dysfunction. Other alternatives might include the broad spectrum of novel drug candidates targeting hyperglycemia now progressing through clinical trials for diabetes (Zaykov et al., 2016) and the exploration of insulin mimetics that readily cross the blood-brain barrier (Jiang et al., 2016; Lawrence et al., 2016).

With this background in mind, it is noteworthy that early clinical trials of intranasal insulin administration as a treatment for AD have yielded encouraging results so far (Craft et al., 2017; Lochhead et al., 2015). Benefits of intranasal insulin delivery include direct, short range and rapid access to the hippocampus and cortex along

perivascular routes independently of crossing the brain-blood barrier (Lochhead et al., 2015), minimal entry of the delivered insulin into the general circulation (Born et al., 2002), and consequently, no systemic hypoglycemia (Claxton et al., 2015). The net results of these exploratory drug trials indicated statistically significant improvements in cognitive tasks, brain volumetrics as determined by MRI, and CSF biomarkers of AD for patients who received intranasal insulin for 4 months (Craft et al., 2017). These preliminary results amply warrant expanding the clinical trials in terms of patient cohort size and insulin administration parameters.

The recent basic science findings about insulin resistance and AD also open additional doors to possible improvements in early diagnosis and therapeutic intervention. For example, TNFα, activated mTOR complexes and tau that has become toxic because of its phosphorylation at the sites required for CCR might serve as early diagnostic signs, especially when considered as individual elements of multiplexed diagnostic assays. Likewise, each of those same markers potentially can serve as therapeutic targets for AD.

The fundamental studies from our group and others suggest compounds that inhibit CCR might be therapeutic candidates to consider. Indeed, preclinical data indicate that cyclin-dependent kinase 4 (Cdk4) inhibitors may be neuroprotective in models of AD (Sanphui et al., 2013). Currently, two Cdk4/6 inhibitors approved by the FDA for cancer, namely palbociclib and ribociclib, might be worth testing as potential AD drugs in the future. Inhibitors of Cdk5 have also been considered as possible therapeutic candidates (Liu et al., 2016), although the currently available ones, such as dinaciclib, seliciclib and AT7519, are promiscuous inhibitors of other cyclin-dependent kinases. There are a number of antibodies that inhibit TNFα and are FDA approved for other diseases, but these face the serious challenge of penetrating the blood-brain barrier. More promising might be small molecule inhibitors targeting TNFα, for which there are some preclinical data suggesting prevention of cognitive loss in transgenic mouse models of AD (Gabbita et al., 2012).

Acknowledgements

The authors collective work on Alzheimer's disease has been supported over the years by the Owens Family Foundation (GSB, and JSL), NIH (grant RF1 AG051085 to GSB), the Cure Alzheimer's Fund (GSB and JSL), the Alzheimer's Association (grants 4079 and ZEN-16-363266 to GSB), Webb and Tate Wilson (GSB), The Virginia Chapter of the Lady's Auxiliary of the Fraternal Order of Eagles (GSB), the University of Virginia President's Fund for Excellence (GSB), and the Alzheimer's and Related Diseases Research Award Fund (grant 17-5 to AN).

References

Arendt, T., Bruckner, M.K., Mosch, B., Losche, A., 2010. Selective cell death of hyperploid neurons in Alzheimer's disease. Am. J. Pathol. 177, 15–20.
Bhaskar, K., Maphis, N., Xu, G., Varvel, N.H., Kokiko-Cochran, O.N., Weick, J.P., Staugaitis, S.M., Cardona, A., Ransohoff, R.M., Herrup, K., Lamb, B.T., 2014. Microglial derived tumor necrosis factor-alpha drives Alzheimer's disease-related neuronal cell cycle events. Neurobiol. Dis. 62, 273–285.
Bloom, G.S., 2014. Amyloid-beta and tau: the trigger and bullet in Alzheimer disease pathogenesis. JAMA neurol. 71, 505–508.
Bomfim, T.R., Forny-Germano, L., Sathler, L.B., Brito-Moreira, J., Houzel, J.C., Decker, H., Silverman, M.A., Kazi, H., Melo, H.M., McClean, P.L., Holscher, C., Arnold, S.E., Talbot, K., Klein, W.L., Munoz, D.P., Ferreira, S.T., De Felice, F.G., 2012. An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease- associated Abeta oligomers. J. Clin. Invest. 122, 1339–1353.
Born, J., Lange, T., Kern, W., McGregor, G.P., Bickel, U., Fehm, H.L., 2002. Sniffing neuropeptides: a transnasal approach to the human brain. Nat. Neurosci. 5, 514–516.
Brown, E.J., Beal, P.A., Keith, C.T., Chen, J., Shin, T.B., Schreiber, S.L., 1995. Control of p70 s6 kinase by kinase activity of FRAP in vivo. Nature 377, 441–446.
Carrero, I., Gonzalo, M.R., Martin, B., Sanz-Anquela, J.M., Arevalo-Serrano, J., Gonzalo-Ruiz, A., 2012. Oligomers of beta-amyloid protein (Abeta1-42) induce the activation of cyclooxygenase-2 in astrocytes via an interaction with interleukin-1beta, tumour necrosis factor-alpha, and a nuclear factor kappa-B mechanism in the rat brain. Exp. Neurol. 236, 215–227.
Claxton, A., Baker, L.D., Hanson, A., Trittschuh, E.H., Cholerton, B., Morgan, A., Callaghan, M., Arbuckle, M., Behl, C., Craft, S., 2015. Long-acting intranasal insulin detemir improves cognition for adults with mild cognitive impairment or early-stage Alzheimer's disease dementia. J. Alzheimers Dis. 44, 897–906.
Craft, S., 2007. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. Curr. Alzheimer Res. 4, 147–152.
Craft, S., Claxton, A., Baker, L.D., Hanson, A.J., Cholerton, B., Trittschuh, E.H., Dahl, D., Caulder, E., Neth, B., Montine, T.J., Jung, Y., Maldjian, J., Whitlow, C., Friedman, S., 2017. Effects of regular and long-acting insulin on cognition and Alzheimer's disease biomarkers: a pilot clinical trial. J. Alzheimers Dis. 57, 1325–1334.
de la Monte, S.M., 2014. Type 3 diabetes is sporadic Alzheimer's disease: mini-review. Eur. Neuropsychopharmacol. 24, 1954–1960.
De Felice, F.G., Vieira, M.N.N., Bomfim, T.R., Decker, H., Velasco, P.T., Lambert, M.P., Viola, K.L., Zhao, W.Q., Ferreira, S.T., Klein, W.L., 2009. Protection of synapses against Alzheimer's-linked toxins: insulin signaling prevents the pathogenic binding of A beta oligomers. Proc. Natl. Acad. Sci. U. S. A. 106, 1971–1976.
Gabbita, S.P., Srivastava, M.K., Eslami, P., Johnson, M.F., Kobritz, N.K., Tweedie, D., Greig, N.H., Zemlan, F.P., Sharma, S.P., Harris-White, M.E., 2012. Early intervention with a small molecule inhibitor for tumor necrosis factor-alpha prevents cognitive deficits in a triple transgenic mouse model of Alzheimer's disease. J. Neuroinflammation 9, 99.
Jiang, P., Dong, Z., Ma, B., Ni, Z., Duan, H., Li, X., Wang, B., Ma, X., Wei, Q., Ji, X., Li, M., 2016. Effect of vanadyl rosiglitazone, a new insulin-mimetic vanadium complexes, on glucose homeostasis of diabetic mice. Appl. Biochem. Biotechnol. 180, 841–851.
Lawrence, C.F., Margetts, M.B., Menting, J.G., Smith, N.A., Smith, B.J., Ward, C.W., Lawrence, M.C., 2016. Insulin mimetic peptide disrupts the primary binding site of the insulin receptor. J. Biol. Chem. 291, 15473–15481.
Liu, S.L., Wang, C., Jiang, T., Tan, L., Xing, A., Yu, J.T., 2016. The role of Cdk5 in Alzheimer's disease. Mol. Neurobiol. 53, 4328–4342.
Lochhead, J.J., Wolak, D.J., Pizzo, M.E., Thorne, R.G., 2015. Rapid transport within cerebral perivascular spaces underlies widespread tracer distribution in the brain after intranasal administration. J. Cereb. Blood Flow Metabol. 35, 371–381.
Norambuena, A., Wallrabe, H., McMahon, L., Silva, A., Swanson, E., Khan, S.S., Baerthlein, D., Kodis, E., Oddo, S., Mandell, J.W., Bloom, G.S., 2017. mTOR and neuronal cell cycle reentry: how impaired brain insulin signaling promotes Alzheimer's disease. Alzheimers Dementia 13, 152–167.
Ozes, O.N., Akca, H., Mayo, L.D., Gustin, J.A., Maehama, T., Dixon, J.E., Donner, D.B., 2001. A phosphatidylinositol 3-kinase/Akt/mTOR pathway mediates and PTEN antagonizes tumor necrosis factor inhibition of insulin signaling through insulin receptor substrate-1. Proc. Natl. Acad. Sci. U. S. A. 98, 4640–4645.
Pei, J.J., Bjorkdahl, C., Zhang, H., Zhou, X., Winblad, B., 2008. p70 S6 kinase and tau in Alzheimer's disease. J. Alzheimers Dis. 14, 385–392.
Sanphui, P., Pramanik, S.K., Chatterjee, N., Moorthi, P., Banerji, B., Biswas, S.C., 2013. Efficacy of cyclin dependent kinase 4 inhibitors as potent neuroprotective agents against insults relevant to Alzheimer's disease. PLoS One 8, e78842.
Seward, M.E., Swanson, E., Norambuena, A., Reimann, A., Cochran, J.N., Li, R., Roberson, E.D., Bloom, G.S., 2013. Amyloid-beta signals through tau to drive ectopic neuronal cell cycle Re-entry in Alzheimer's disease. J. Cell Sci. 126, 1278–1286.
Shaw, L.M., Korecka, M., Clark, C.M., Lee, V.M., Trojanowski, J.Q., 2007. Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. Nat. Rev. Drug Discov. 6, 295–303.
Steen, E., Terry, B.M., Rivera, E.J., Cannon, J.L., Neely, T.R., Tavares, R., Xu, X.J., Wands, J.R., de la Monte, S.M., 2005. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease–is this type 3 diabetes? J. Alzheimers Dis. 7, 63–80.
Varvel, N.H., Bhaskar, K., Patil, A.R., Pimplikar, S.W., Herrup, K., Lamb, B.T., 2008. Abeta oligomers induce neuronal cell cycle events in Alzheimer's disease. J. Neurosci. Off. J. Soc. Neurosci. 28, 10786–10793.
Villemagne, V.L., Burnham, S., Bourgeat, P., Brown, B., Ellis, K.A., Salvado, O., Szoeke, C., Macaulay, S.L., Martins, R., Maruff, P., Ames, D., Rowe, C.C., Masters, C.L., 2013. Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. Lancet neurol. 12, 357–367.
West, M.J., Coleman, P.D., Flood, D.G., Troncoso, J.C., 1994. Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease. Lancet 344, 769–772.
Zaykov, A.N., Mayer, J.P., DiMarchi, R.D., 2016. Pursuit of a perfect insulin. Nat. Rev. Drug Discov. 15, 425–439.
Zhao, W.Q., De Felice, F.G., Fernandez, S., Chen, H., Lambert, M.P., Quon, M.J., Krafft, G.A., Klein, W.L., 2008. Amyloid beta oligomers induce impairment of neuronal insulin receptors. Faseb J. 22, 246–260.
Zoncu, R., Efeyan, A., Sabatini, D.M., 2011. mTOR: from growth signal integration to cancer, diabetes and ageing. Nat. Rev. Mol. Cell Biol. 12, 21–35.