

The implication of the brain insulin receptor in late onset Alzheimer's disease dementia

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Alzheimer's disease (AD) is progressive neurodegenerative disorder characterized by brain accumulation of the amyloid β peptide ($A\beta$), which form senile plaques, neurofibrillary tangles (NFT) and, eventually, neurodegeneration and cognitive impairment. Interestingly, epidemiological studies have described a relationship between type 2 diabetes mellitus (T2DM) and this pathology, being one of the risk factors for the development of AD pathogenesis. Information as it is, it would point out that, impairment in insulin signalling and glucose metabolism, in central as well as peripheral systems, would be one of the reasons for the cognitive decline. Brain insulin resistance, also known as Type 3 diabetes, leads to the increase of $A\beta$ production and TAU phosphorylation, mitochondrial dysfunction, oxidative stress, protein misfolding, and cognitive impairment, which are all hallmarks of AD. Moreover, given the complexity of interlocking mechanisms found in late onset AD (LOAD) pathogenesis, more data is being obtained. Recent evidence showed that $A\beta_{42}$ generated in the

brain would impact negatively on the hypothalamus, accelerating the 'peripheral' symptomatology of AD. In this situation, A β 42 production would induce hypothalamic dysfunction that would favour peripheral hyperglycaemia due to down regulation of the liver insulin receptor. The objective of this review is to discuss the existing evidence supporting the concept that brain insulin resistance and altered glucose metabolism play an important role in pathogenesis of LOAD. Furthermore, we discuss AD treatment approaches targeting insulin signalling using anti-diabetic drugs and mTOR inhibitors. © 2018 by the authors. Licensee MDPI, Basel, Switzerland.

Alzheimer's

Amyloid

Cognition

Insulin receptor

Insulin resistance

TAU

Type 2 diabetes

amyloid beta protein[1-42]

antidiabetic agent

beta secretase 1

glucose transporter 4

insulin

insulin receptor

insulinase

mammalian target of rapamycin inhibitor

oligomer

protein kinase B

tau protein

transcription factor FOXO

Alzheimer disease

Article

cognition

dementia

disease association

down regulation

glucose metabolism

human

hyperglycemia

hypothalamus disease

insulin resistance

insulin signaling

nerve degeneration

non insulin dependent diabetes mellitus

nonhuman

outcome assessment

pathogenesis

protein function

protein localization

protein phosphorylation

total quality management