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CNS & Neurological Disorders - Drug Targets, 2016, *15*, 000-000

Insulin and the Future Treatment of Alzheimer's Disease

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Abstract: Alzheimer's disease is a neurodegenerative disorder leading to dementia. Scientific efforts in the last decade focused mainly on understanding pathophysiology of disease and possible pharmacological approach to alleviate cognitive decline symptoms. Amyloid cascade hypothesis though criticized, remains the leading hypothesis to understand pathogenic mechanisms of cognitive decline. Intriguingly, changes of metabolic activity of cortical neurons are associated with reduced or absent sensitivity to insulin in Alzheimer's disease brain. Insulin is a multipotent hormone regulating, not only glucose levels, but also cell survival and synaptic plasticity mechanisms of neurons. Replacement of insulin might represent a new strategic approach to counteract neurodegeneration. Here we review most of the available data regarding relationship between Alzheimer's disease and insulin and propose new direction to deepen our understanding about insulin involvement in the pathogenesis of Alzheimer's dementia.

Keywords: Alzheimer's Disease, Diabetes mellitus, insulin, neurodegeneration Amyloid Beta, tau.

Received: October 31, 2015 **Revised: December 11, 2015** **Accepted: December 15, 2015**

INTRODUCTION

Alzheimer's Disease (AD) is one of the most frequent neurodegenerative disorders worldwide. It is an age-related disease responsible for progressive cognitive decline and dementia. Although pathologically represented by two distinct hallmarks, namely the extracellular senile plaques and the intracellular neurofibrillary tangles, pathophysiological mechanisms of AD are partly known, tremendously complex, and still matter of debate. To date researchers agree that most of the pathological changes observed in AD are linked to the so-called "amyloid hypothesis" [1]. Amyloid precursor protein (APP) is a membrane glycoprotein physiologically synthesized and localized at synaptic level although with unclear function. So far, APP has been demonstrated to play a role in stabilization of synapses during sustained neurotransmission, and this seems to be particularly important for N-Methyl-D-Aspartate (NMDA) excitatory synapses [2-4]. APP is physiologically degraded by secretases in soluble and unsoluble peptides, via two main pathways namely the amiloidogenic and non-amiloidogenic [1]. Both pathways are in equilibrium. Unsoluble peptides produce, the ABeta peptides (Aβ), which are then metabolized by two peptidases, degrading enzymes, the Insulin Degrading Enzyme (IDE) and Neprilysin, in order to control any accumulation [5, 6]. IDE has recently attracted much of interest because it is involved in cleavage of both insulin and Aβ, since that a potential link between AD and Diabetes Mellitus type II (DM II) pathogenesis has been suggested. The impairment of the physiological metabolism of APP, due to unknown causes to date, would lead to the progressive accumulation of Aβ. These are able to aggregate filaments, fibrils and plaques, and changes responsible for neurodegeneration in AD brains. In particular, the overproduction of Aβ is associated with the formation of intermediate species, oligomers, with highly toxic effects on synaptic membranes [7, 8]. Oligomers interfere with neuro-transmitters activity, in particular with the cholinergic and the glutamatergic, inducing disequilibrium in the homeostasis of genes and metabolic pathways signaling involved in synaptic plasticity mechanisms and memory formation on one side, and those involved in aberrant signaling, synaptic

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