Diabetes & Metabolic Syndrome: Clinical Research & Reviews 10S (2016) S144–S149

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

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

Review

Shared links between type 2 diabetes mellitus and Alzheimer's disease: A review

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ARTICLE INFO

Keywords:
Alzheimer's disease
Type 3 diabetes
Type 2 diabetes mellitus
Shared links

ABSTRACT

Epidemiological studies have proved that, there are pathophysiological connections between Type 2 Diabetes Mellitus (T2DM) and Alzheimer's disease (AD). Diabetic patients have higher incidences of cognitive impairment and hence they are more at the risk of developing AD. Some of the recent evidences have majorly stated the effects of insulin resistance in the disturbance of various biological processes and signaling pathways. Both hyperglycemia and hypoglycemic conditions contributes in dysfunctioning of cognitive abilities and functions. The present review summarizes the evidences which establish the possible links between the two pathologies on the account of molecular, biochemical and at histopathological level. The information regarding their interactions was collected from different databases and journals. The gathered information will clearly establish the link among the two pathologies and will be helpful in future for the development of drugs for Type 3 Diabetes.

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Contents

1. Introduction

Type 2 diabetes mellitus (T2DM) is rapidly growing etiology among the population. With the improvement in treatment strategies and extensive care of diabetes people have significantly increased the survival rate. So, a major portion of population are living longer with diabetes and dealing with its complications [1]. Alzheimer's disease (AD), a type of dementia that leads to abnormalities at biochemical, histopathological and at molecular level is one of the emerging complications of T2DM [2]. The studies have shown that risk of developing AD is increased by 50–60 percent in case of T2DM [3].

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http://dx.doi.org/10.1016/j.dsx.2016.01.021
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The association between AD and T2DM is complex and the key components of their relationship are insulin resistance and inflammatory signaling pathways. Studies have shown and proved that AD cases with T2DM results in hyperphosphorylation of tau protein, abnormal regulation in the clearance process of amyloid beta, higher levels of cortical IL-6 and high frequency of micro vascular infarcts in comparison to the non diabetic AD cases [4,5].

In T2DM, insulin signal gets impaired that results in the deposition of amyloid-β (APP-Aβ) plaques, mitochondrial dysfunction, inflammatory stress in peripheral tissue. Such common features are also seen in the AD patients but the mechanisms of their interactions are not clearly understood [6]. Experimental evidences have shown that impaired glucose metabolism results in early abnormalities in cognitive abilities.

On the contrary to this, some previous study reports that T2DM cases with AD had less neurofibrillary tangles (NFT) and fewer neuritic plaques both in cerebral cortex and in hippocampal region [7]. The possible explanation for this research was the presence of soluble amyloid beta oligomers that leads to the desensitization of insulin which had shown to inhibit the intracelluar Aβ release [8]. In contrast, other have shown that the amyloid deposition was significantly higher in diabetes with ApoE4 allele than non-diabetic patients [9,10]. By the evaluation of some older literature it has been found that, some of majorly involved receptors of T2DM such as insulin/IGF-1 receptors are concerned with the expression and phosphorylation of tau gene [11]. With the disturbance in their expression affects various others receptors downstream to it and contributes to T3D. Such complex signaling pathways are activated in various target organs and connect AD with T2DM.

All the above mentioned factors arose the concept of relationship between the altered insulin signaling and the cognitive impairment, hence the term Type 3 Diabetes (T3D) was proposed for T2DM induced AD [12,13]**.** So, T3D was defined as critical situation of insulin resistance that eventually induces AD.

In the current review, we have discussed the role of majorly involved pathophysiological links that transfer the pathology of T2DM to AD. So that in future, researchers can design drugs targeting effective link to manage T3D.

2. Shared connections between T2DM & AD

The specific link between the two pathologies is still not known but the possible links from the older literature are discussed here (Fig. 1).

2.1. Impaired insulin/insulin receptors

Earlier it was believed that the uptake of glucose in brain was insulin independent, as GLUT-1 and GLUT-3 are insulin insensitive glucose transporters in brain. Now, studies reported that there is some insulin receptors which are insulin sensitive present both in certain neuronal cells and at the blood brain barrier [14]. The uptake of glucose into the brain is a saturable process but when the uptake of glucose increases in the brain, it would require the upregulation of insulin receptors. But when this receptors activity compromised, it could lead to functional hypoglycemia that reduces the glucose metabolism rate in brain, defining features of AD. On the other hand, if the glucose is entering normally in the brain but the amount of insulin is not adequate, it would lead to the formation of glycated end products. Insulin plays a crucial role in cognitive functions. If insulin is administered acutely, it will improve the memory and cognition functions but if it is administered chronically it will affect the cognition abilities that lead to insulin resistance, inflammation and hyperglycemia. Also, it decreases the sensitivity of insulin at blood brain barrier and hence affects the glucose metabolism in brain. So, in this situation when the energy fuel is inside the body but the brain cells are unable to utilize it, starvation of brain cells occurs [15,16].

2.2. ChAT

Studies have shown that Braak stage of AD is associated with the reduced level of choline acetyl transferase (ChAT) expression which results in decreased immunoreactivity of ChAT with insulin or IGF-1 receptor in cortical neurons. Experimental data have demonstrated that the tau protein and ChAT gene expression are controlled by insulin and IGF-1 receptor [17]. Therefore, insulin resistance or deficiency contributes to brain plasticity, synaptic dysfunction, and neurodegeneration and decreases the production of acetylcholine which possibly establishes a biochemical link between Diabetes mellitus and AD by impairing the cognitive abilities [18].

2.3. ADDL

Amyloid beta- derived diffusible ligands (ADDL) contribute to insulin deficits and insulin resistance in the brain of AD patients. As they are small, so easily diffusible due to which it becomes more harmful than amyloid beta. They cause dysfunctioning by disrupting the mechanism of memory formation, as it breaks the communication link between the insulin and its receptor at the synapse. ADDLs itself binds to the synapse and change its

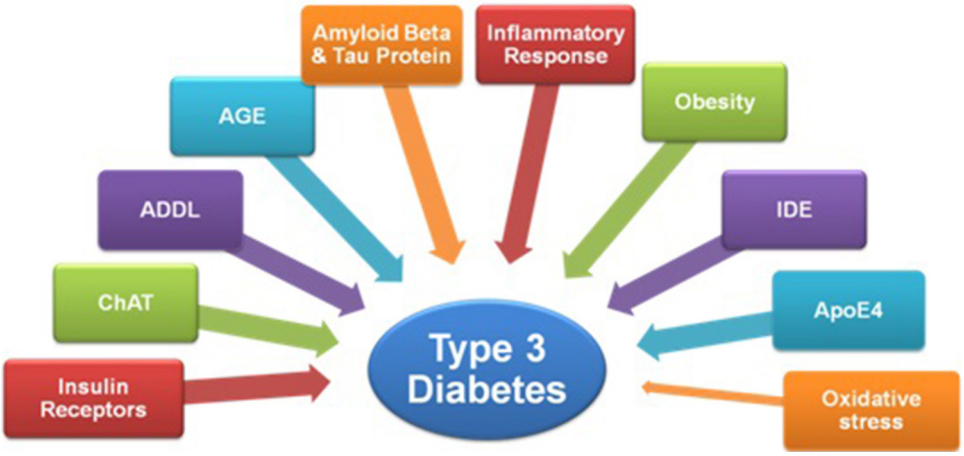

Fig. 1. Factors responsible for development of Type 3 Diabetes pathology.

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