

Alzheimer's Disease & Treatment

Chapter 6

Type 2 Diabetes Mellitus: A Risk Factor for Alzheimer's Disease

Ruchi Jakhmola Mani¹; Khyati Mittal¹; Deepshikha Pande Katare^{1,*}

¹Proteomics and Translational Research Lab, Centre for Medical Biotechnology, Amity Institute of Biotechnology, Amity University Uttar Pradesh and Noida, India. 201303.

*Correspondence to: Deepshikha Pande Katare, Professor, Assistant Director, Head Centre for Medical Biotechnology, Amity Institute of Biotechnology, Amity University Uttar Pradesh, Noida, India. 201313

Email: dpkatare@amity.edu

Abstract

Alzheimer's disease (AD) and Type 2 Diabetes Mellitus (T2DM) are two most damaging endocrine disorders. T2DM patients are at a higher risk of developing dementia of AD type later in their lives and therefore this shift in pathology should be closely monitored. Insulin resistance is a common phenomenon in both T2DM and AD and is the probable triggering process in this pathology. The insensitivity to glucose sensing in brain causes eventual loss of neurons, increased inflammation and stress. In this chapter, we have discussed the common molecular links between T2DM and AD and have covered the route of progression of T3D. Chapter later describes the common molecular pathways and processes and some druggable protein targets in these pathways.

Keywords: Alzheimer's disease; Type 2 Diabetes; Type 3 Diabetes; Protein interactions; Druggable targets.

1. Introduction

AD is a serious threat to mankind and is ranked number one in the list of most prevalent neurodegenerative disease [1]. It is estimated that more than 5.8 million Americans are suffering with AD and it is expected to increase up to 13.8 million by 2050 [2]. AD is a type of dementia that leads to abnormalities in normal functioning of brain. It is characterized by biochemical, histopathological and molecular abnormalities, and deposits of amyloid- β , excessive cell loss,

dystrophic neuritis, mitochondrial dysfunction, neurofibrillary tangles, endoplasmic reticulum stress, DNA damage and oxidative stress [3]. To date AD remains an incurable disease because its aetiology is still not clear. Various risk factors have already been identified which may provide insight into the basics of AD pathology for its better understanding. So far, aging is considered to be significant reason behind the disease, but recently T2DM is also considered to be one of the major risk factor of AD [4].

T2DM is a metabolic disease which is also known as non-insulin dependent diabetes. According to the reports of IDF diabetes atlas eighth edition, 425 million adults are living with diabetes globally and it is estimated that it will increase up to 629 million by 2045 [5]. Several evidences suggest that insulin resistant/insulin insensitivity is involved in AD as well. Latest researches have discussed (i) insulin sensitivity in AD[6]; (ii) MCI in exploratory animal models of T2DM [7, 8];(iii) experimental animal models and humans with improved cognitive functions after the treatment with intranasal insulin; [6,9];(iv) common biochemical, mechanistic, biochemical and histopathological abnormalities in AD and T2DM [10,11];(v) higher risk of developing mild cognitive impairment (MCI) (vi) AD in people suffering with T2DM [12,13].

Although, there are very few reports which suggested that T2DM is associated with AD but there were no scientific evidences to support this theory [14,15]. Katare and co-workers (2016) have published for the first time a link between T2DM and AD and deciphered, a closest route between T2DM linked AD and named it as Type 3 Diabetes (T3D) [16]. Animal models have been used as a tool from historic times in the investigation and characterization of disease pathology, target identification and in the evaluation of therapeutic agents. In this chapter we have discussed the concept of T2DM to AD progression and explained the pathways behind these linked pathologies. Probable drug targets for T3D are also covered.

2. Is Type 2 Diabetes Mellitus a Risk Factor for Alzheimer's disease?

T2DM and AD are metabolic disorders and now they have become a serious threat to human health. The study by Alzheimer's Association had reported amylin deposits in pancreatic islets of Langerhans cells in T2DM patients but its role remained unresolved [17]. The study further mentioned that amylin fibril formation results in dysfunction of pancreatic beta cells and is the major cause of death in T2DM [18]. T2DM is already an expensive disease and incurred around USD 727-billion-dollar expenditure in 2017. This disease is exponentially rising every year and has become a matter of serious concern (19). The risk factors associated with T2DM are explained in **(Figure 1)**.

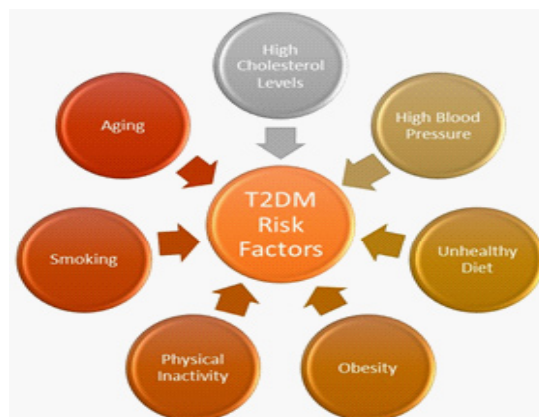


Figure 1: Risk factors for Type 2 Diabetes Mellitus

Around 50-75% percent T2DM population is at risk of developing dementia in comparison to the patients having only insulin resistance [20]. It is independent of the presence of APOE4 gene due to which T2DM induced AD is believed to be sporadic [9]. Since the incidence of T2DM has increased worldwide and is expected to reach 592 million by 2035 [21, 22]. It is evident that T2DM induced AD cases might rise in coming years [9].

AD contributes to the 60-80% of total dementia cases [22]. In AD, brain plaques are formed as a result of uneven cleaving and mis-folding of protein amyloid precursor protein (APP), found in the membrane of the neurons along with three other proteolytic enzymes such as alpha-secretase, beta-secretase and gamma-secretase [23]. These plaques inhibit the synaptic transmission of acetylcholine from one nerve cell to the other and hence neurons start degrading. It has been recently reported that there are some nerve-cell surface proteins (PirB and LirB2) which act as receptors for beta-amyloid and hence these fragments get deposited near neurons and interfere with its normal functioning [23]. Tangles are formed due to hyper phosphorylation of tau protein which in less phosphorylated form, gives strength to the neuronal structure by binding to microtubules and help in neuronal communication.

Currently sporadic AD cases are on the rise and associated risk factors for AD are given in (Figure 2).



Figure 2: Risk factors for Alzheimer's disease

T2DM and AD patients have similar amyloid beta deposits in pancreas as well as in brain [9]. Scientists have identified proteins which were common to both pathologies. They

used neuronal Butyrylcholinesterase (BChE) as reference protein and found three group of sequences BChE precursor K allele (NP_000046.1), Acetylcholinesterase (AChE) isoform E4-E6 precursor (NP_000656.1), and apoptosis-related acetylcholinesterase (AChE) that might play an influential role in both the pathologies. Few reviews are available that has mentioned the common links between T2DM and AD. Our group has also published a review on shared links between T2DM and AD [24] which extensively covers all the research and review papers highlighting the link between T2DM and AD. A study by Li and co-workers (2015) has suggested that anti diabetic agents might be effective in treating AD [24]. Similarly, another study by Sridhar and his team (2015) has mentioned that not only improvement in lifestyle measures has shown protective effects in cognitive impairment but some of the antidiabetic agents like metformin, GLP-1 receptor agonists are also helpful in treating AD [25].

3. Understanding Type 3 Diabetes

Insulin is a pancreatic hormone which is involved in the utilization of glucose, regulation of energy metabolism, reproduction and homeostasis. The signaling pathways of insulin are conserved in different cells and tissues. According to Blázquez and coworkers (2014) there could be two possible source of insulin in the brain [26]. Firstly, the peripheral insulin enters into the brain via GLUT (Glucose transporters) transporters present at the blood brain barrier. Secondly, the production of insulin in the brain itself. Therefore, it is believed that there is a constant supply of insulin to the brain. In normal brain, increased glucose level increases the release of insulin which proves that the metabolism of glucose in the brain is similar to that of pancreas. This insulin activates insulin receptors present at the blood brain barrier which helps in the normal functioning of the brain [27].

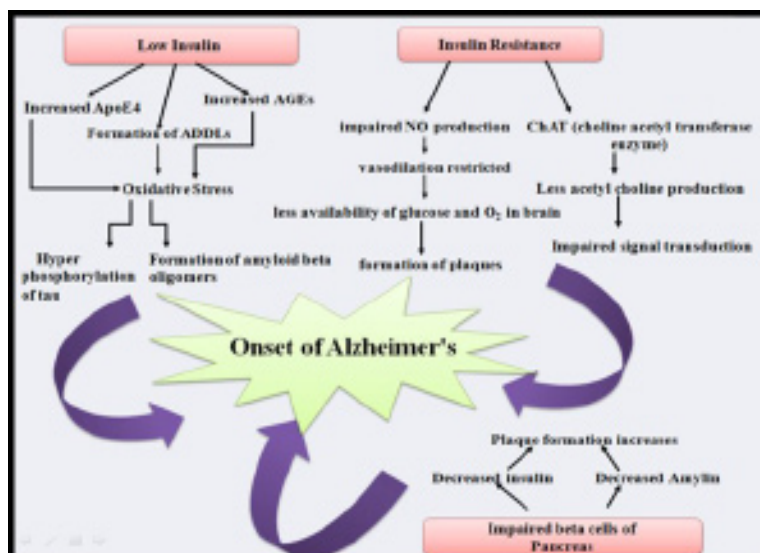


Figure 3: Schematic representation of progression of Type 2 diabetes mellitus to Alzheimer's disease

The binding of insulin to insulin receptor further activates the Insulin Receptor Substrate-1(IRS1), extracellular signal-related kinase/mitogen-activated protein kinase (ERK/MAPK), and PI3kinase/AKT pathways (PI3K/AKT) and inhibits glycogen synthase kinase-3beta (GSK-3 β), results in the regulation of all these signaling pathways for the proper functioning of whole system[9]. Dysregulation of any of these pathways can lead to other complications such as pancreatic cancer,

nephropathy, neuropathy etc. [28]. Also, it could add to other issues such as oxidative stress, mitochondrial dysfunction in the neuronal cells [28].

Probable hypothesis explaining the possible progression of T2DM to AD is displayed in **Figure 3** [16]. In T2DM induced AD condition, the insulin binding to its receptor gets inhibited due to insulin resistance. This results in hyper phosphorylation of tau protein and deposition of amyloid plaques both in brain and pancreas. Low insulin or insulin resistance results in the formation of ADDL, AGEs and increases the activity of APOE4. All these factors produce high level of oxidative stress in the brain which increases the risk of onset of AD [29].

The correlation studies between the T2DM and AD indicate the cross talk between the proteins from both pathologies. In T2DM conditions, pancreatic beta cells are functional and produced insulin but these cells lose their ability to recognize insulin, as a result level of insulin increases in blood and starts damaging beta cells. Consequently, the level of insulin starts depleting in the body. Low insulin level and high blood sugar affects the cognitive and learning abilities of a person which is similar to the condition of Alzheimer's patients [29].

4. Plausible Linked Processes Between Type 2 Diabetes Mellitus and Alzheimer's disease

The plausible linked processes between T2DM and AD were extensively studied by Katare and co-workers (2016) and an understanding for possible progression of T3D was proposed in (**Figure 4**).

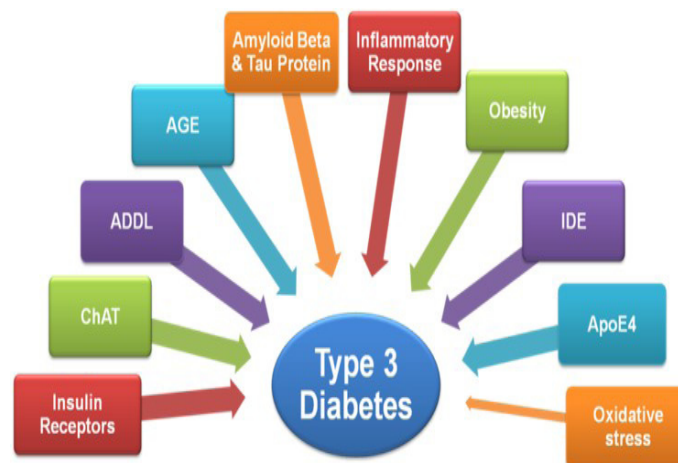


Figure 4: Factors culprable for development of Type 2 Diabetes Mellitus induced Alzheimer's disease pathology (Source: Mittal et. al., 2016) [24]

(i) Impaired receptors

It was reported that the GLUT-1 and GLUT-3 transporters are insulin independent carriers present in brain, due to which the uptake of glucose become independent to insulin. Researchers have suggested that there are receptors which are sensitive to insulin and are located in the blood brain barrier [30]. The glucose uptake in brain is regulated by glucose homeostasis which is maintained by saturation of glucose on both sides. Hence, whenever

the consumption of glucose in brain increases, the over expression of insulin receptors is required. But when INSR receptors activity is decreased, it possibly reduces the rate of glucose metabolism that will result in functional hypoglycaemia.

(ii) Inflammatory response

Insulin resistance is the key aspect of T2DM which is linked with the increase levels of inflammatory mediators like 1-antichymotrypsin, C-reactive protein and interleukin-6 (IL-6). These exalted levels of inflammatory markers are associated with the dysfunction of immunological responses. These inflammatory byproducts accumulate in Alzheimer's affected brain at different rate. It is reported that C-reactive protein is highly associated with the possibility of developing AD. Antidiabetic drug like PPARG agonists (peroxisome proliferator-activated receptor G) have the ability to not only reduce the insulin resistance but also minimize the IL-6 levels in AD thereby capable of decreasing the incidence of AD and T2DM.

(iii) Obesity

Obesity can increase the risk of AD by directly influencing the brain pathology via hypertension or impaired insulin signaling pathway. It may lead to impaired glucose metabolism, dyslipidaemia, insulin resistance and hypertension. All these factors are critical precursor of T2DM. Numerous reports have demonstrated that the possibility of AD is 3 folds higher in obese patients not suffering from T2DM. There is direct relation between the waistcircumference and hippocampal atrophy. It means those AD patients having higher circumference of the waist will have lower HDL concentration and plasma concentrations of triglycerides and glucose. It has already been reported that every 15% rise in body mass index at older age i.e. above 65 years can escalate the risk of developing AD by 37%.

(iv) Choline acetyl transferase (ChAT)

The Braak stages in AD pathology are linked with decreased level of ChAT expression. The reduced immune response of ChAT also decreases the activity of insulin or IGF-1 receptors in cortical neurons. Thus, impaired insulin signaling and low insulin results in dysfunctioning at synapse, brain plasticity and reduces the acetylcholine production which potentially builds up a biochemical connection among T2DM and AD by affecting the memory and learning abilities [31].

(v) Oxidative stress

Oxidative stress plays a vital role in both the disorders and establishes a significant link between them. An imbalance in reactive oxygen species, nitrogen species, free radicals, H_2O_2 causes oxidative damage to lipids, nucleic acids and proteins. AGEs and ALE (advanced lipid peroxidation products) serve as the biomarkers in the progression of T2DM and AD.

RAGE(receptors of advanced glycation end products)acts as receptor interacts with beta amyloid peptides and causes cognitive impairment.

(vi) Amyloid beta-derived diffusible ligands (ADDLs)

ADDLs add to shortfalls of insulin in AD brains. These ligands are smaller in size due to which they can easily diffuse which turns out to be more damaging than amyloid beta. It results in dysregulation of the system of memory development. It damages the connection between the insulin and its receptor. It ties to the neural connection and alter its conformation. It results in the adjustment of state of synapse and decreases the insulin binding affinity for its receptor. ADDLs are connected to the system of AD as it has appeared to bring about synaptic loss, hyper phosphorylation of tau protein, high level of inflammation and reduced plasticity [6]. Since, ADDLs influences insulin signaling mechanism, hence it was proposed that it could be the major reason of brain diabetes.

(vii) Advanced glycation end products (AGE)

The probable link through which T2DM connected with AD is the improved generation of AGEs. These are the outcome of events of Malliard reaction. In normal aging process, AGEs accumulate in different cell sorts however their aggregation rate essentially increased in diabetic and additionally in AD patients [32, 33]. These aggregated glycated end products results in the formation of neurofibrillary tangles and deposition of amyloid beta plaques [32].

(viii) Amyloid beta & tau protein

The closeness amongst AD and T2DM exhibits the accumulation of amyloid beta plaques in brain and in pancreas. Pancreatic cells produce and release both amylin and insulin. Studies have reported that increased levels of amyloid disturb the glucose homeostasis, and affect the functioning of beta cells [34]. Beta secretase improperly cleaves the amyloid precursor protein which results in the deposition of plaques. This unusual amyloid beta interacts with different signaling pathways and hyper phosphorylated the tau protein. Glycogen synthase kinase-3 beta (GSK-3 β) assumed a noteworthy part in the phosphorylation of tau protein [35]. In this way, hindrance of GSK-3 β could be the druggable target for the treatment of T3D (**Figure 5**).

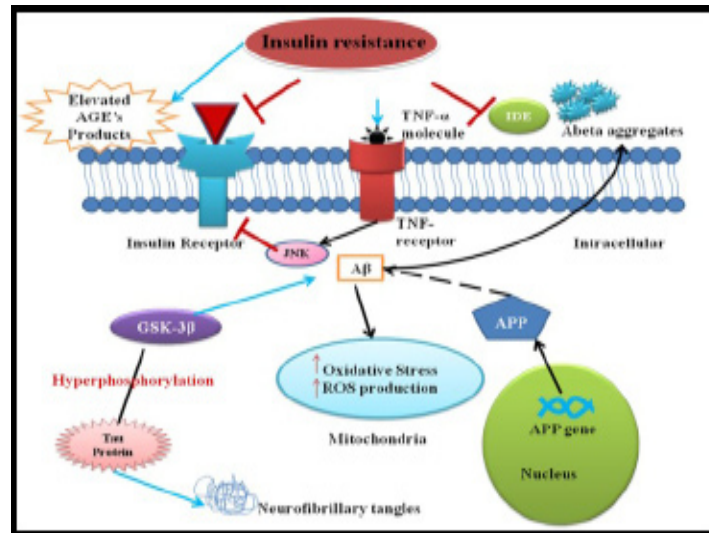


Figure 5: Diagrammatic depiction impaired insulin signaling affected pathways (Source: Mittal et al., 2016) [24]

5. Protein Interactions and Druggable Targets in Type 3 Diabetes

Epidemiological studies have repetitively verified the links between T2DM and AD [1]. It is also suggested that late-stage AD is more consistently associated with incipient to moderate T2DM condition [3]. Even though there are varied conclusions regarding the relationship between T2DM and AD, it is far and wide accepted that T2DM is linked with poor cognition. In comparison to healthy individuals, T2DM patients tend to perform poorer on attention, memory, cognition, and normal functioning [12]. A study by Katare and co-workers (2016) have demonstrated the nine different routes (Figure 6) by which T2DM can progress to AD and named their pathology as T3D [16].

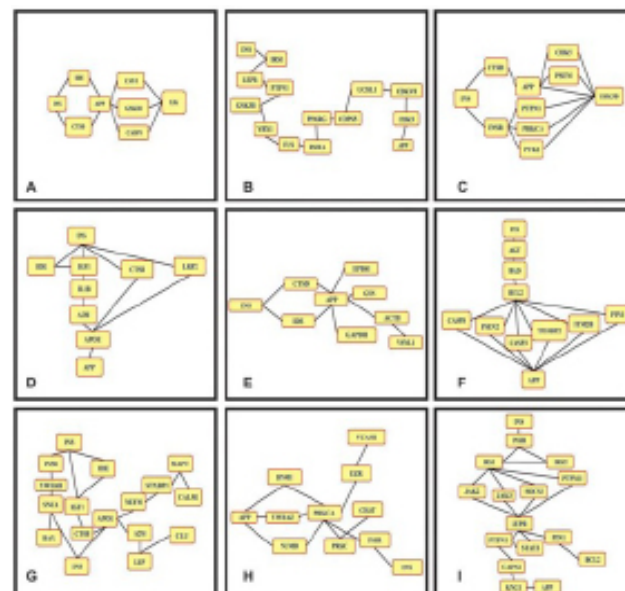


Figure 6: The figure depicts the several routes for progression of T3D. These short routes represent the mechanism which connects both the insulin and amyloid beta (Source: Mittal et al., 2016) [16]

It was observed that the proteins involved in T3D were executing major roles in molecular processes and pathways like, Chemokine Pathway, INS, MAPK, JAK-STAT, T-Cell differentiation, Apoptosis, p53 pathway, SCLC etc. (16). Some of the proteins in these routes are mutated in T2DM condition (red nodes) and therefore pose a higher risk towards conversion of T2DM to AD (**Figure 7**).

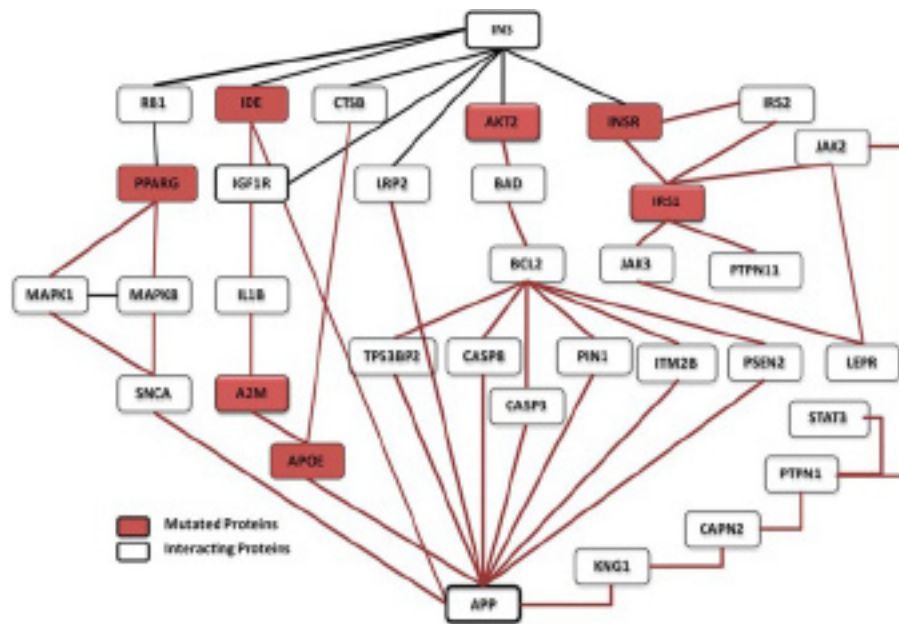


Figure 7: Protein- interaction network depicting all nine routes of progression from T2DM to AD (T3D)(Source: Mittal et al., 2016) [16]

Some of the proteins displaying higher degree of network interaction like IRS1, IDE, PPARG, BCL2, APP, A2M, APOE etc. have potential to work as druggable targets and can be studied further in preclinical and clinical studies for their validation in T3D.

6. Animal Models Developed For Drug Discovery and Development

(I) Type 2 Diabetes Mellitus Model

Rat/mouse model of T2DM are divided into two categories one is obesity model and other is non-obesity model. Majority of obese models mimic the pathology initiated due to genetic or dietary problems. However, this type of model is also associated with other pathologies such as atherosclerosis, dyslipidaemia, neuropathy and nephropathy [36]. A number of diabetic animal models have been developed of which rodent models are the most appropriate one. Rodent models are divided mainly into two main categories i) spontaneous diabetic model ii) non spontaneous diabetic model. Chemically induced non-spontaneous models are more popular than genetically induced diabetic models because of their low cost, easy induction of diabetes, easy maintenance and higher availability. Most of the experimentally induced diabetes were developed in last 30 years mainly include adult STZ/alloxan rat model, neonatal model of STZ/alloxan, high fat diet induced STZ model, pancreatectomy models of diabetes, chronic STZ diabetic model [37]. Below are some of the rodent models developed using different chemicals (**Table 1**).

Table 1: Chemically induced Diabetes animal model (Source: Tripathiet al., 2014) [38]

Chemicals	Effect
STZ	It prevents the synthesis of DNA in mammalian cells. It enters the pancreatic cells and causes alkylation of DNA. It also activates the release of nitric oxide and polyadenosine diphosphate ribosylation. Necrosis destroys the pancreatic beta cells.
Alloxan	Its treatment leads to sudden release of insulin followed by complete destruction of islet cells. Alloxan reacts with thiol groups in the glucose binding site and inactivates the enzyme. It produces reactive oxygen species (ROS) and superoxide radicals.
Dithizone	It has abilities to infuse membranes. It can complex zinc in the liposomes along with the release of H ⁺ ions. It increases the diabetogenicity. Release of proton and insulin solubilisation would induce osmotic stress and rupture granules.
Gold thioglucose	It developed obesity induces diabetes. It impaired the secretion of insulin in the early phase and also reduces the insulin level in pancreatic beta cells.
Monosodium glutamate	Once ingested, it results in large insulin reaction.

(II) Alzheimer's Disease Model

One of the important features for the animal model of AD is the behavioral analysis. In the field of neuroscience, rat exhibits good scientific features for study of neuroimaging, neurosurgical manipulations, histopathology and many more [4]. Rat model is much more accurate and similar to human pathology than the mouse models for AD. As an AD model, rat is an important tool for the study of behavior, memory impairment and to study the effect of cholinesterase inhibitors. We have enlisted some of the chemically induced AD models in (Table 2).

Table 2: Chemically induced Alzheimer's disease model [4]

Chemically induced animal models	Mechanism of action	Effects
Scopolamine induced memory deficit	<ul style="list-style-type: none"> It blocks the binding site of acetylcholine (ACh) muscarinic receptors in cortex 	<ul style="list-style-type: none"> Memory and learning impairment in dose dependent manner
Colchicine's induced memory impairment	<ul style="list-style-type: none"> It elevates the glu/GABA ratio in brain cortex causing hyper-activation of NMDA receptors and increased calcium influx. 	<ul style="list-style-type: none"> It causes decline in dopamine, nor-adrenaline, serotonin in cerebral cortex, caudate nucleus and hippocampus
Alcohol induced diabetes	<ul style="list-style-type: none"> It produces NO excessively which impairs memory and learning, whereas higher doses of ethanol interfere with glutamatergic system and enhance GABAergic transmission in memory related areas of brain. It also increases the extracellular level of adenosine leading to memory impairment 	<ul style="list-style-type: none"> It causes hippocampus and cholinergic neurons impairment, affects sensory-motor system, disrupts memory and learning

STZ	<ul style="list-style-type: none"> • STZ impairs the glycolytic enzyme activity in brain which leads to decline in ATP and creatine phosphate level. • It reduces the synthesis of acetyl CoA that results in defects in cholinergic transmission 	<ul style="list-style-type: none"> • STZ causes ROS and RNS production induces neuronal damage and tau hyperphosphorylation.
L-Methionine induced dementia	<ul style="list-style-type: none"> • Chronic homocysteine level causes changes in cerebral blood vessels producing impaired cerebral perfusion, oxidative stress and decrease in nitric oxide (NO) bioavailability 	<ul style="list-style-type: none"> • Hyperhomocysteinemia also causes vascular dementia and also neurotoxicity by NMDA hyper-excitation leading to tau hyperphosphorylation and Aβ deposits
Excitotoxins, neurotoxins, cholinotoxins induced memory deficit	<ul style="list-style-type: none"> • Ibotenic acid is an excitotoxin as it is a NMDA receptor agonist causing calcium overload in neurons and neuronal toxicity 	<ul style="list-style-type: none"> • It caused oxidative damage (increase lipid peroxidation, nitrite concentration, and decrease in SOD level) in the hippocampus.
Sodium azide induced dementia	<ul style="list-style-type: none"> • It is an inhibitor of mitochondrial respiratory chain, causing excitotoxicity • It generates free radicals, inhibition of aerobic energy metabolism leading to neurodegeneration and APP dysfunctioning 	<ul style="list-style-type: none"> • It affects the enzyme acetylcholine transferase (AChT) causing lesser cholinergic inputs but no loss of cholinergic neurons. • It produces the memory and learning impairment
Heavy metal induced dementia	<ul style="list-style-type: none"> • It produces reactive oxygen species (ROS) in brain leading. • It also causes tau hyperphosphorylation and apoptosis leading to neuronal toxicity in the hippocampus 	<ul style="list-style-type: none"> • Aluminium exposure leads to cognitive dysfunction and damage the oxidative stress parameters.
Benzodiazepine induced memory deficit	<ul style="list-style-type: none"> • cause suppression of Long Term Potentiation (LTP) which is involved in maintaining learning and memory 	<ul style="list-style-type: none"> • It causes retrograde amnesia.

7. Conclusions

AD is an irreversible neurological disorder, which has affected a major portion of the society. In addition to this, T2DM induced dementia of AD type is increasing the economic burden of the countries. There are few reports which indicated that T2DM is associated with AD but there were no scientific evidences to prove this theory. This T2DM induced AD is termed as T3D. The hypothesis of establish link between T2DM and AD was reported for the first time by Mittal et al., (2016) which T3D. To date there are no such animal models available which can mimic the exact mechanism of action and differentiate between AD, T2DM and T3D. Many research groups have worked on modelling this new type of pathology i.e. T3D in animal models but we still need an extensive and good animal model which can mimic the exact human pathology and differentiate between AD, T2DM and T3D and establish the switch between all these three pathologies. These experimental models can then add more to the list of probable protein receptors which can be targeted to either stop the switch between T2DM and AD or treat T3D. Network studies report involvement of IDE, IRS1, BCL2, APOE, PPARG as probable receptors in this pathology shift.

8. Acknowledgement

We acknowledge Dr. Ashok K Chauhan for providing us the excellent infrastructure and constant motivation. Authors also acknowledge the never-ending support of Ms. Nitu Dogra and Ms. Richa Raj in proofreading this chapter.

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