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"A COMPREHENSIVE REVIEW OF TYPE-3 DIABETES MELLITUS AND ALZHEIMER'S DISEASE"

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is increasingly recognized as a significant risk factor for cognitive decline and various forms of dementia, particularly Alzheimer's disease (AD) and vascular dementia. Despite substantial research, the exact mechanisms that underpin these associations remain elusive. This review delves into the intricate connections between T2DM and cognitive impairments, emphasizing the molecular and cellular features common to T2DM, type 1 diabetes mellitus (T1DM), and insulin resistance. These conditions are linked to memory deficits and cognitive decline, which has led some researchers to suggest that Alzheimer's disease be described as "Type 3 diabetes."

INTRODUCTION

In the last decades, both diabetes mellitus and Alzheimer's disease (AD) are constantly increasing. Affected individuals, therefore,

represent an enormous problem for the society, governments and global organizations. These diseases are usually considered as independent conditions, but increasing evidence shows that there are links between these two disorders. Some pathogenesis factors are shared by type 2 diabetes and Alzheimer's disease: chronic inflammation, oxidative stress, mitochondrial dysfunction, adiponectin deficiency, different expression of plasma cholinesterase activity and vascular damage could represent a possible explanation for the coexistence of these two conditions in many patients.[1] Cognitive dysfunction is increasingly recognized as an important comorbidity of diabetes mellitus. Different stages of diabetes-associated cognitive dysfunction can be discerned, with different cognitive features, affected age groups, prognosis, and likely also different underlying mechanisms. Relatively subtle, slowly progressive cognitive decrements occur in all age groups. More severe stages, particularly mild cognitive impairment (MCI) and dementia, with progressive deficits, occur primarily in older individuals. Evolving insights from studies on risk factors, brain imaging, and neuropathology provide important clues on mechanisms. Although both the risk of clinically diagnosed Alzheimer's disease and that of vascular dementia is increased in association with diabetes.[2] Type 2 diabetes has been consistently associated with an increased risk of dementia, including Alzheimer's disease and vascular dementia; mild cognitive impairment, which is a condition preceding dementia; and cognitive decline, which is the progressive clinical hallmark of dementia.[1] Establishing whether type 2 diabetes is specifically associated with the biological features of Alzheimer's disease or other causes of dementia and ascertaining whether the mechanisms that link type 2 diabetes to dementia can suggest new approaches to dementia treatment have been fraught areas of research. The link between type 2 diabetes and cognitive dysfunction is largely consistent, and a large body of studies on animals and humans point toward biological mechanisms of type 2 diabetes that could be potentially actionable. Given this evidence and in light of the accelerating rates of type 2 diabetes worldwide, establishing the effect of type 2 diabetes on the brain and neurodegenerative diseases is necessary.[3]

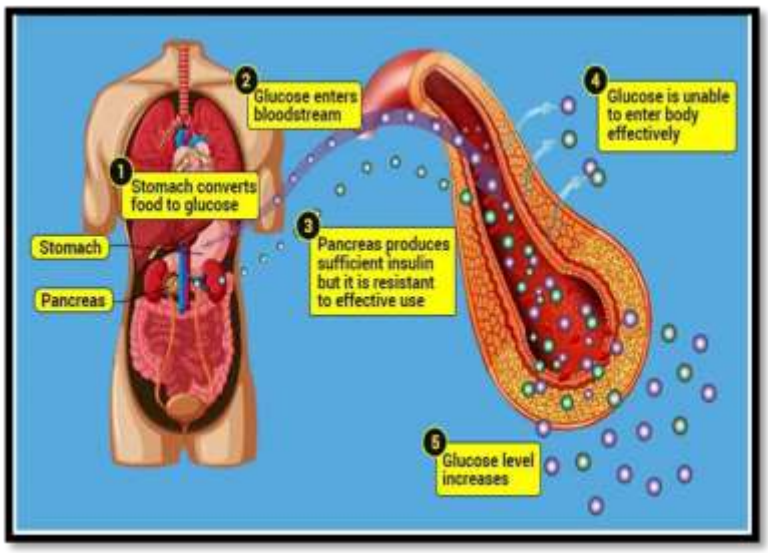

Figure No. 1:Glucose leval increse in bloodstream.

Type 2 diabetes mellitus and late-onset Alzheimer's disease – dementia are increasing in global prevalence and current predictions indicate they will only increase over the coming decades. These increases may be a result of the concurrent increases of obesity and aging. Type 2 diabetes mellitus is associated with cognitive impairments and metabolic factors, which increase the cellular vulnerability to develop an increased risk of age-related late-onset Alzheimer's disease. How type 2 diabetes mellitus increases the vulnerability of the brain's neurovascular unit (NVU), neuroglia and neurons are as follows: aging (chronic age-related diseases), metabolic (hyperglycaemia advanced glycation end products and its receptor interactions, and hyperinsulinaemia – insulin resistance, oxidative stress, inflammation, vascular and microvascular NVU/neuroglial remodelling) with resulting impaired cerebral blood flow.[4] Diabetes mellitus, also called diabetes, is a term for several conditions involving how your body turns food into energy. When you eat a carbohydrate, your body turns it into a sugar called glucose and sends that to your bloodstream. Your pancreas releases insulin, a hormone that helps move glucose from your blood into your cells, which use it for energy. When you have diabetes and don't get treatment, your body doesn't use insulin like it should. Too much glucose stays in your blood, a condition usually called high blood sugar. This can cause health problems that may be serious or even life-threatening. There's no cure for diabetes. But with treatment and lifestyle changes, you can live a long, healthy life. Diabetes comes in different forms, depending on the cause.

Prediabetes

Prediabetes is when your blood sugar is higher than it should be but not high enough for your doctor to diagnose diabetes. More than a third of people in the United States have it, but most of them don't know it. Prediabetes can make you more likely to get type 2 diabetes and heart disease. Exercising more and losing extra pounds, even as little as 5% to 7% of your body weight, can lower those risks.[5]

Type 1 Diabetes

Type 1 diabetes is also called insulin-dependent diabetes. It used to be called juvenile-onset diabetes, because it often begins in childhood. Type 1 diabetes is an autoimmune condition. It happens when your body attacks your pancreas with antibodies. The organ is damaged and doesn't make insulin. Your genes might cause this type of diabetes. It could also happen because of problems with cells in your pancreas that make insulin. Many of the health problems that can come with type 1 happen because of damage to tiny blood vessels in your eyes (called diabetic retinopathy), nerves (diabetic neuropathy), and kidneys (diabetic nephropathy). People with type 1 also have a higher risk of heart disease and stroke. Treatment for type 1 diabetes involves injecting insulin into the fatty tissue just under your skin. You might use.[6]

Type 2 Diabetes

Type 2 diabetes used to be called non-insulin-dependent or adult-onset diabetes. But it's become more common in children and teens over the past 20 years, largely because more young people are overweight or obese. About 90% of people with diabetes have type 2.When you have type 2 diabetes, your pancreas usually creates some insulin. But either it's not enough or your body doesn't use it like it should. Insulin resistance, when your cells don't respond to insulin, usually happens in fat, liver, and muscle cells. Type 2 diabetes is often milder than type 1. But it can still cause major health complications, especially in the tiny blood vessels in your kidneys, nerves, and eyes. Type 2 also raises your risk of heart disease and stroke. People who are obese -- more than 20% over their target body weight for their height -- have an especially high risk of type 2 diabetes and the health problems that can follow. Obesity often causes insulin resistance, so your pancreas has to work harder to make more insulin. But it's still not enough to keep your blood sugar levels where they should be. Treatment for type 2 diabetes involves keeping a healthy weight, eating right, and exercising.

Some people need medication, too. Your doctor might do an A1C test a few times a year to see how well you've been controlling your blood sugar.[7]

DIABETIC MELLITUS:- Diabetes mellitus, also known as diabetes, occurs when the pancreas doesn't produce enough insulin or the body doesn't use it properly, causing glucose to build up in the bloodstream. This leads to high blood sugar, or hyperglycemia, which can cause health problems over time.

The exact cause of most types of diabetes is unknown, but some factors that may contribute to type 2 diabetes include

- Being overweight or obese
- Not getting enough exercise
- Genetics
- Family history
- Being 45 years or older
- Having prediabetes
- Having ever had gestational diabetes
- Giving birth to a baby who weighed more than 9 pounds
- Race or ethnicity

Some risk factors for type 2 diabetes include

- Storing fat mainly in the abdomen
- Having a waist circumference above 40 inches for men and 35 inches for women
- Being physically active for less than 150 minutes a week

Type 3 diabetes is a way of describing Alzheimer's disease.

Type 3 diabetes is a way of describing Alzheimer's disease that is caused by insulin resistance in the brain. Symptoms of type 3 diabetes include

- Memory loss that affects daily living and social interactions
- Difficulty completing familiar tasks
- Misplacing things often
- Decreased ability to make judgments based on information
- Sudden changes in personality or demeanor
- Other symptoms include:
- Losing weight without trying to

- Stomach pain
- Feeling more tired than usual
- Frequently passing wind
- Diarrhea
- Fatty or oily stools
- Hypoglycemia , also called low blood sugar
- Increased thirst
- Frequent urination
- Blurred vision
- Numbness or tingling in the hands or feet
- Slow-healing sores or cuts
- Frequent skin and/or vaginal yeast infections

The signs to look out for can include

- Losing weight without trying to.
- Stomach pain.
- Feeling more tired than usual.
- Frequently passing wind.
- Diarrhea.
- Fatty or oily stools.
- Hypoglycemia, also called low blood sugar.

Type 3 diabetes?

Some research studies have suggested that Alzheimer's disease should also be classified as a type of diabetes, called type 3 diabetes. However, type 3 diabetes is not currently an official medical term. It is not recognized by national health organizations or the American Diabetes Association.

This "type 3 diabetes" is a term proposed to describe the hypothesis that **Alzheimer's disease** is caused by a type of insulin resistance and insulin-like growth factor dysfunction that occurs specifically in the brain. This condition also has been used by some to describe people who have T2D and also receive a diagnosis of Alzheimer's disease. The classification of type 3 diabetes is highly controversial, and it's not widely accepted by the medical community as a clinical diagnosis. Another classification of diabetes includes type 3c diabetes mellitus (also called T3cDM, pancreatogenic diabetes, and type 3c diabetes). This

type of diabetes develops due to conditions that affect the pancreas. Despite having a similar name, this is a separate condition.

Diagnosis of type 3 diabetes

- neurological examination
- medical history
- Neurophysiologic testing
- Dementia.

Treatment for type 3 diabetes

There's no one treatment for type 3 diabetes, as it is not an official diagnosis.

There are separate treatment options for people who have

- Prediabetes
- T2D
- Alzheimer's disease

A doctor may recommend lifestyle measures, such as diet and exercise.

A doctor may also recommend certain lifestyle measures that may include.

Managing weight: Doctors may recommend weight loss for some people with diabetes. If you are overweight, a doctor may recommend methods to help you lose around 7%Trusted Source of your body mass. This can help stop organ damage caused by high blood sugar and may prevent the progression of prediabetes to T2D, according to the National Institute of Diabetes and Digestive and Kidney Diseases.

Balancing diet: A diet low in fat and rich in fruits and vegetables can help improve symptoms.

Quitting smoking if you smoke: Avoiding smoking may help you manage your condition.

If you have T2D and Alzheimer's, managing diabetes may also help slow the progression of dementia.

Researchers are investigating a possible link between metformin, a diabetes medication, and Alzheimer's disease.

Some research Trusted Source suggests that the drug may have a protective effect against Alzheimer's disease while other research Trusted Source suggests metformin may increase a person's risk for Alzheimer's disease. Additional studies are needed to understand the relationship between this drug and neurodegenerative disease.

Medications for Alzheimer's disease

Prescription medications may treat cognitive symptoms of dementia, but there's uncertainty about whether they have a noticeable impact on the symptoms of Alzheimer's disease. Medications prescribed to people with Alzheimer's disease can include.

Anti-amyloid antibody intravenous infusion therapy, such as aducanumab (Aduhelm) and lecanemab (Leqembi), which may remove beta-amyloid from the brain to reduce cognitive and functional degeneration in people in the early stages of Alzheimer's disease.

Acetylcholinesterase inhibitors, such as donepezil (Aricept), galantamine (Razadyne), or rivastigmine (Exelon), which may improve the way that your body's cells communicate with one another.

Memantine (Namenda), an NMDA-receptor antagonist, may also help reduce symptoms and slow the progression of Alzheimer's disease.

Doctors may treat symptoms of Alzheimer's disease, like mood changes and depression, with psychotropic drugs. Antidepressants and anti-anxiety medications are part of treatment in some cases.

Some people may need antipsychotic therapy later in the disease course.

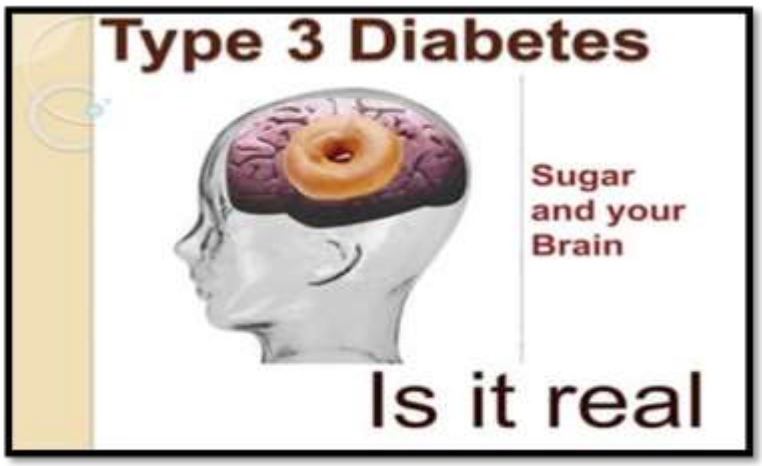

Figure No. 2: Type-3 diabetes and brain (alzheimer's).

Theory/Methodology Used

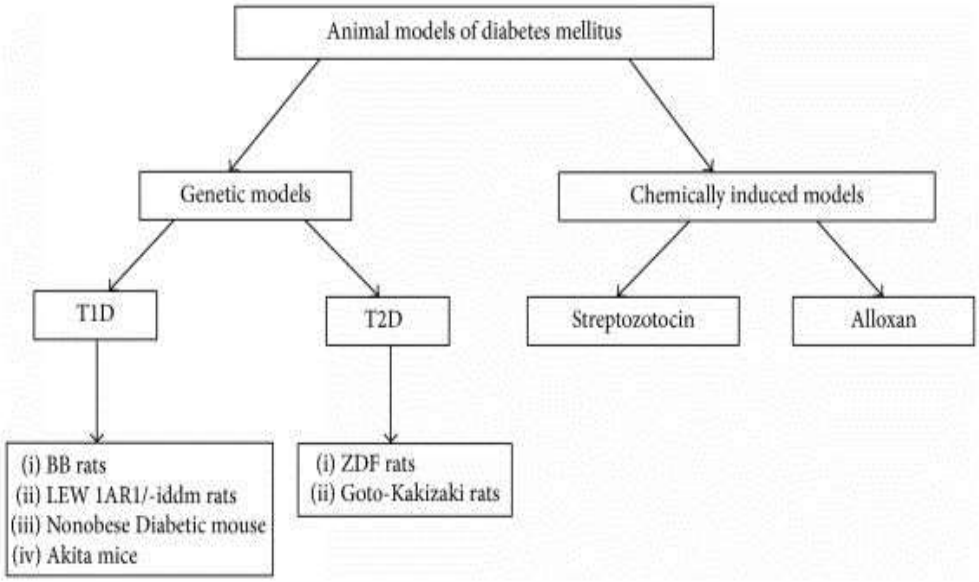

Figure No. 3: Animal modules for diabetes mellitus.

Animal models of diabetes mellitus

A) Genetic models

I) T1D

a) BB rates (bio-breeding rat)

b) LEW 1ARI/iddm rats (Insulin-dependent diabetes mellitus)

c) Nanobese diabetic mouse

d) Akita mice

II) T2D

a) ZDF rats (Zucker diabetic Fatty rat.)

b) Goto-kakizaki rats

Chemically induced models

I) Steptozotocin

II) Alloxan

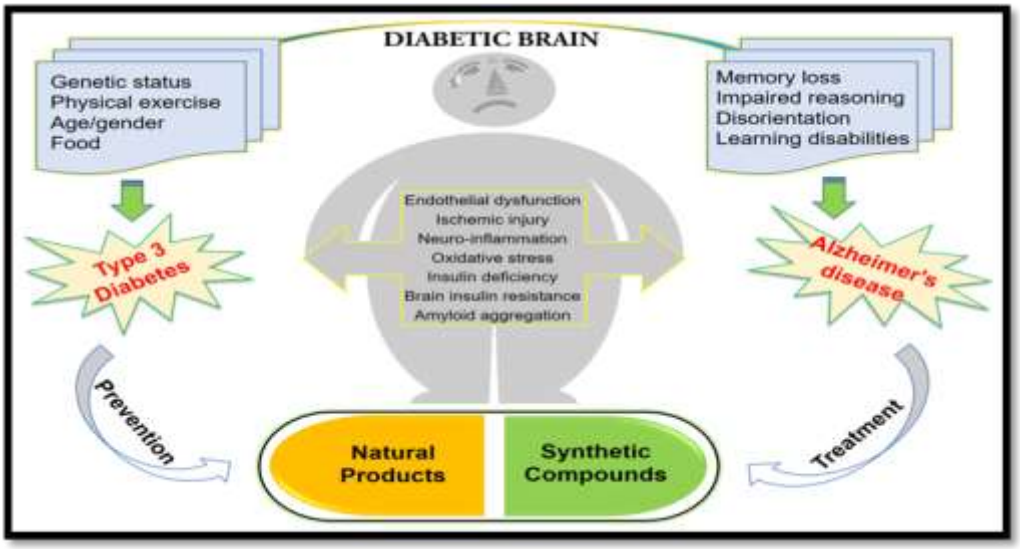

Figure No. 4: Type-3 diabetes and alzheimer's disease.

Highly inbred with a limited number of pathways to T1D, therelevance to human T1D has been questioned.[9] In type2 diabetes (T2D) mellitus, numerous animal models havebeen developed for understanding the pathophysiology ofdiabetes and its complications.[10] These animal models tendto include models of insulin resistance and/or models of betacell failure. On the other hand, several T2Danimalmodels areobese, reflecting the humanconditionwhere obesity is closelylinked to T2D development. Most of these models tend tohave abnormalitiesin a single gene or multiple genes relatedto obesity, glucose intolerance, and/or insulin resistanceleading to high blood glucose levels.[11]

Zucker Diabetic Fatty (ZDF) Rats

Thediscovery of this type of rats occurred in 1961 after a cross of *Merck (M-strain)* and *Sherman* rats.They are characterizedby a mutated leptin receptor that induces hyperphagia and the rats become obese by 4 weeks of age.[12] These rats arehyperinsulinemic, hyperlipidemic, and hypertensive as well and show impaired glucose tolerance.[13] The homozygous mutation (fa/fa) of the leptin hormone receptor results in the development of type 2 diabetes in male rats when they are fed a high-energy rodent diet. These rats develop advanced insulin resistance and glucose intolerance between 3 and 8 weeks of age and turn overtly diabetic between 8 and 10 weeks of age with glucose levels in the feeding state typically 500mg/dL by 10 to 11 weeks of age. Evidence suggests that there is a good consistency between the increase in islet DNA content and serum insulin levels indicating that islet hyperplasia plays a role in the development of hyperinsulinemia in *Zucker Diabetic*

Fatty (ZDF) rats.[14] Triglycerides and cholesterol levels in obese rats are higher than those observed in lean rats.

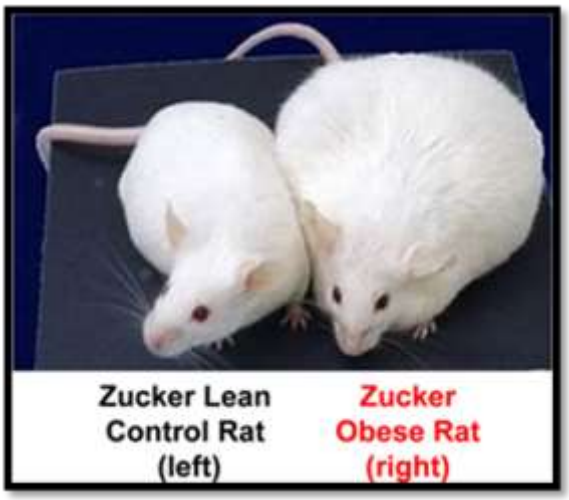

Figure No. 5: Zucker lean rat & fatty rat.

BB Rats

This type of rat was derived from out bred *Wister rats*. Firstly, spontaneous autoimmune diabetes was identified in 1974 in a Canadian colony and then led to the creation of two founder colonies from which all substrains have been derived including one of inbred *Biobreeding Diabetes-Prone/Worcester (BBDP/Wor)* and one of out bred *Biobreeding Diabetes-Prone (BBDP) rats.*[22] It was reported that immunologically and genetically distinct *BB rat* substrains were derived from several tertiary *Biobreeding (BB) rat* colonies[23] including *Biobreeding/Ottawa Karlsburg (BB/OK) (BB/Pfd)* and *Biobreeding Spontaneously Hypertensive Rats (BB.SHR).*[24–27] Additionally, *BB rats* resistant to diabetes have been bred to act as controls. After puberty, *Biobreeding (BB) rats* develop diabetes with a similar incidence between males and females with about 90% of rats developing diabetes between eight and sixteen weeks of age. The diabetic phenotype is quite severe and is characterized by development of hyperglycemia, hypoinsulinemia weight loss, and ketonuria requiring insulin therapy for survival. The latter clinical and metabolic symptoms are preceded by histological abnormalities in the islets of pancreas. It was concluded that the earliest detectable anomaly is the enhanced expression of interferon-α (IFN-α) and major histocompatibility complex (MHC) class I molecules in islet cells, which occur soon after weaning followed by progressive infiltration of islets by macrophages, natural killer (NK) cells, dendrite cells, T cells and to a lesser extent B cells.[28–30]

Figure No. 6: BB rat An-Animal model T1D.

LEW 1AR1/-iddm Rats

(ZDF-Leprfa/Crl). This rat model of type 1 diabetes (T1D) arose spontaneously in a colony of congenic Lewis rats characterized by a defined MHC haplotype *Lewis.1AR1 (LEW.1AR1) rat.* It is a unique model for studying human T1D in which rats were being bred in Hannover Medical School (Ztm) at the Institute of Laboratory Animal Science and obtained as a result of a spontaneous mutation in the *LEW.1AR1* strain. It was obvious that these rats develop diabetes between 60 and 90 days of age and are characterized by rapid progression of insulitis leading to extensive β cell destruction.[50] These rats are distinct from the well-characterized *Nonobese Diabetic (NOD)* model of T1D as, unlike *Biobreeding Diabetes-Prone (BBDP) rats*, diabetes develops with equal frequency in both male and female animals.[49] Studies clearly showed that the incidence of diabetes in these animals is increased from 20% to 60% with further inbreeding with equal incidence in both genders[49]; moreover, the animals also display a prediabetic state that lasts for approximately a week with islet infiltration.[41] The *Lewis-insulin dependent diabetes mellitus (LEW-iddm) rats* are able to survive well after diabetes is overtly shown and, consequently, they can be used as a model to study diabetic complications.[53] These animals are ketonuric, but they are not lymphopenic expressing normal numbers of ART2+ T cells. Furthermore, β cells of the islets of Langer Hans of affected animals are infiltrated with B and T lymphocytes, macrophages, and natural killer (NK) cells and it appears that the beta cells die via apoptosis.[22] They show apoptotic beta cell destruction induced by pro inflammatory cytokines that are released from islet-infiltrating immune cells.[49] In *Lewis.1AR1-insulin dependent diabetes mellitus (LEW.1AR1-*

iddm) rat, the diabetic syndrome displays an autosomal recessive mode of inheritance with an incomplete penetrance of the mutant phenotype of about 60%.[50]

Figure No. 7: Lewis inbred rat.

Goto-Kakizaki Rats

Developing mild hyperglycaemia at an early stage of life, the *Goto-Kakizaki (GK)* rat is considered a nonobese model. This type 2 diabetes (T2D) model originates from *Wistar (W)* rat established by repeated inbreeding with *Wistar (W)* rats at the upper limit of normal distribution for glucose tolerance[46] with most likely glucose intolerance due to impaired *β* cell mass and function on the background of a polygenic inheritance. Chronic exposure to hyperglycemia (glucotoxicity) may further impair *β* cell function and insulin action and contribute to the development of hyperglycemia. However, insulin resistance contributionmay likely be secondary in the development of hyperglycemia in this model. *Goto-Kakizaki (GK) rat* pancreatic islets may develop into the so-called starfish-shaped islets characterized by disrupted structure with clear fibrosis separating strands of endocrine cells making the islets resemble the appearance of a starfish. These changes are not present in the pancreas of young *GK rats* but increase in prevalence with aging.[48] In adult *Goto-Kakizaki (GK) rats*, total pancreatic *β* cell mass and pancreatic insulin stores are similarly decreased by 60%.[49] This alteration in the *β* cell population cannot be attributed to increased *β* cell apoptosis but is rather related, at least in part, to marked decrease in *β* cell replication.[49] Theonset of a profound alteration in glucose estimulated insulin secretion by the *GK β* cell, after weaning, correlates with the exposure to the diabetic environment. These changes in the islet function may result, at least in part, from a loss of differentiation of *β* cells chronically exposed to even mild chronic hyperglycemia and elevated plasma nonesterified fatty acids, a process referred to as "glucolipotoxicity." According to a previous study conducted in our

laboratory using *GK rats* as a diabetic model, measurement of oral glucose tolerance test (OGTT) revealed that blood glucose concentration peaked at 60min after glucose administration and then began to decrease. Basal blood glucose level was significantly lower than that after the oral glucose tolerance test (OGTT) pointing to the impairment of carbohydrate homeostasis. Furthermore, the study revealed that hyperglycemia in *GK rats* can be moderated by exercise, where exercise promotes the prevention and treatment of type 2 diabetes (T2D) because of the increase in the capacity of the muscles to capture circulating glucose due to the decreased intramuscular fat reserves. Running *Goto-Kakizaki (GK) rats.*

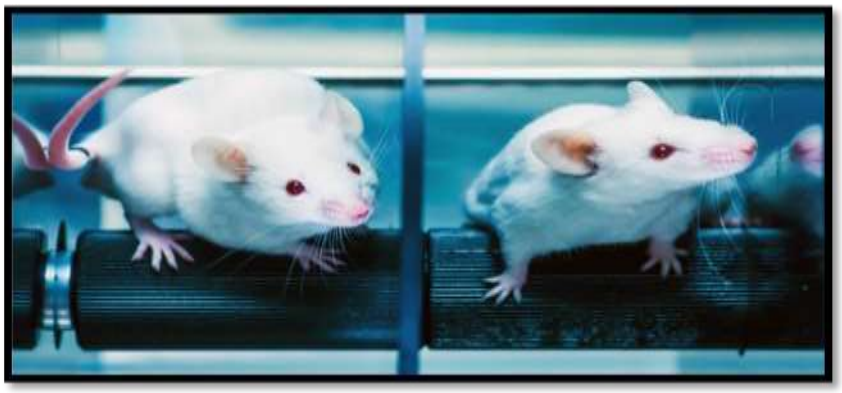

Figure No. 8: Goto-Kakizaki Rats T2D model.

Chemically Induced Diabetes

Alloxan and streptozotocin (STZ) are considered the most potent diabetogenic chemicals used in diabetes research so far Both chemicals are employed as cytotoxic glucose analogues that tend to accumulate in pancreatic beta cells through glucose transporter 2 (GLUT2).[49]

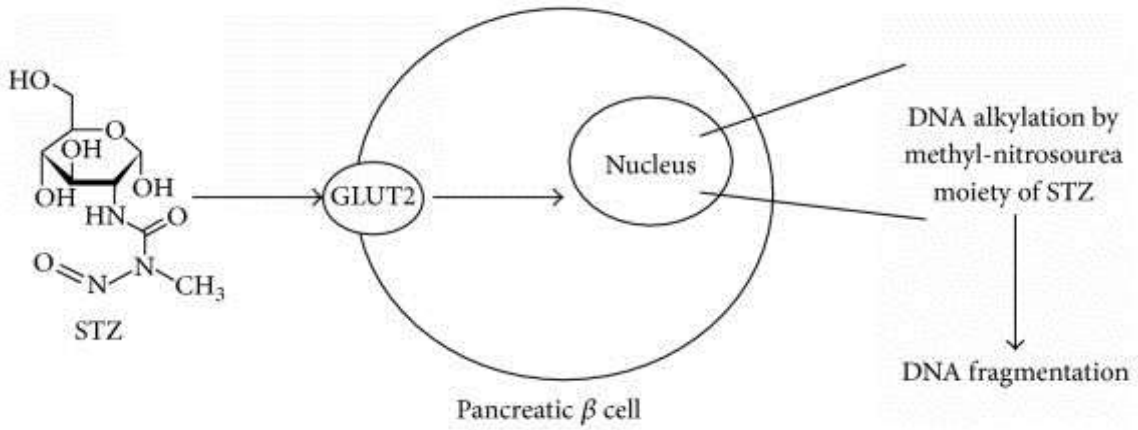

Figure No. 9: Mechanism action of streptozotocin.

STZ acts as a nitrosourea analogue, in which there is linkage between the N-methyl-N-nitrosourea (MNU) moiety and carbon-2 of hexose.[49] In general, the mode of action of toxicity of STZ depends on the DNA alkylating activity of Its methyl-nitrosourea moiety.[49] The transfer of the methyl group from STZ to the DNA molecule causes damage along a defined chain of events[49] and leads to DNA fragmentation[49] (Figure 9). STZ-induced diabetes is of two types: the adult type and neonatal type. In case of the adult type streptozotocin- (STZ-) induced diabetes, rats weighing 140 to 300 g underwent a single streptozotocin (STZ) intraperitoneal injection (45–70mg/kg) dissolved in 0.1M citrate buffer (pH 4.5) after an overnight fast. Control rats of the same age received only an injection of citrate buffer. A number of studies with STZ-induced diabetes mellitus reported that diabetes mellitus can improve the recovery of cardiac function after ischemia-reperfusion[49] along with decreasing the incidence of arrhythmias.[49] It was previously contended that the contractile function of diabetic hearts following ischemia-reperfusion recovered to a greater extent than that of the control hearts. However, the magnitude of the preischemic basal contractile function was significantly reduced in the diabetic hearts.[49] Protein kinase C (PKC) inhibitors were found to restore the impaired cardiac function in diabetes before ischemia; however, PKC inhibitors completely abolished protection against postischemic injury in diabetic hearts.[49] This effect of protein kinase C inhibition in diabetes may be explained by the decreased phosphorylation of myocardial proteins (e.g., troponin).[49]. Chen et al. have found that severe.

hyperglycemia due to diabetes mellitus induced by STZ decreases the incidence of arrhythmias and increases coronary flow and expression of heat shock protein 90 (hsp90).[49] Nonetheless, the study hypothesized that increased osmolarity due to severe hyperglycemia is in charge of the overexpression of heat shock protein 90 (hsp90), which in turn increases the production of endothelial nitric oxide (NO).[49] Furthermore, it was well addressed that diabetic hearts are much more resistant to ischemia-induced.

arrhythmias compared to nondiabetic controls.[49] It was also noted that, 4 weeks following streptozotocin (STZ) treatment, hearts have improved functional recovery after ischemia-reperfusion in comparison to control hearts and this functional recovery was associated with the prevention of hexokinase solubilization during ischemia.[49]

Future Perspectives

1. Prevention Strategies: Understanding the shared pathophysiological mechanisms between type-3 diabetes mellitus (T3DM) and Alzheimer's disease (AD) could lead to the development of prevention strategies targeting both conditions simultaneously. Lifestyle interventions, such as diet and exercise programs, could be tailored to reduce the risk of cognitive decline in individuals with T3DM.

2. Early Detection and Intervention:-Early detection of cognitive dysfunction in individuals with diabetes could allow for timely interventions to prevent or delay the onset of AD. Routine cognitive screening in diabetic patients could become a standard practice in clinical settings, enabling early diagnosis and management.

3. Precision Medicine:-Advancements in personalized medicine could lead to tailored treatments for individuals with both T3DM and AD. Genetic and molecular profiling could identify subgroups of patients at higher risk for cognitive decline, allowing for targeted interventions and therapies.

4. Therapeutic Targets:- Identifying specific molecular targets shared between T2DM and AD could lead to the development of novel therapeutic agents. Drugs targeting insulin resistance, inflammation, oxidative stress, and amyloid-beta accumulation may hold promise for preventing or treating cognitive impairment in diabetic patients.

5. Multidisciplinary Approaches:- Collaborative efforts between researchers, clinicians, and policymakers are essential for addressing the complex interplay between T2DM and AD. Multidisciplinary research initiatives could facilitate the translation of basic science discoveries into clinical applications and public health interventions.

CONCLUSION

Recent studies suggest that Alzheimer's disease (AD) might be linked to diabetes, which is why some researchers call it "Type 3 diabetes." This idea comes from the fact that problems with insulin and blood sugar in the brain can cause AD symptoms like memory loss and brain cell damage.

The association between type 2 diabetes mellitus and Alzheimer's disease represents a significant health challenge with far-reaching implications for individuals, families, and healthcare systems worldwide. While the precise mechanisms linking these two conditions

are still being elucidated, emerging evidence suggests common pathophysiological pathways involving insulin resistance, inflammation, and neurodegeneration.

Addressing the growing burden of T2DM-associated cognitive dysfunction requires a multifaceted approach encompassing prevention, early detection, personalized treatment strategies, and collaborative research efforts. By leveraging advances in molecular biology, neuroscience, and clinical medicine, there is hope for developing effective interventions to mitigate the impact of T2DM on brain health and reduce the risk of AD in diabetic patients.

Ultimately, a comprehensive understanding of the relationship between T2DM and AD will not only improve clinical outcomes but also inform public health policies aimed at promoting healthy aging and preserving cognitive function in aging populations.

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