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Diabetes and Cognitive Decline: Challenges and Future Direction

Diabetes and Cognitive decline

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Abstract

There is growing evidence that diabetes can induce cognitive decline and dementia. It is a slow progressive cognitive decline that occurs in all age groups of diabetic patients but is seen clearly in older individuals, and the symptom is worsened by chronic metabolic syndrome. Animal models are frequently utilized to elucidate the mechanisms of cognitive decline in diabetes and to assess therapeutic drugs for therapy and prevention. This review will address the common factors and pathophysiology involved in diabetes-related cognitive decline and outline numerous animal models used to investigate diabetic-induced cognitive decline.

Key Words: Diabetes mellitus; animal models; cognitive decline; pathophysiology

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Core Tip: Factors and pathophysiology of diabetes induces cognitive decline involving the fluctuation in glycaemic status, macrovascular and microvascular diseases, deterioration of insulin signaling, neuroinflammation in the brain, mitochondrial dysfunction, increase in the advanced glycation end product (AGE), the effect of drugs

used in the treatment of diabetes and diabetic autonomic dysfunction. Various animal models have been constructed to examine the pathophysiology of diabetes-induced cognitive decline.

INTRODUCTION

According to the International Diabetes Federation (IDF), more than one in every ten persons today has diabetes. Diabetes prevalence among adults (20-79 years old) has more than quadrupled from 151 million (4.6% of the world population) in 2000 to 537 million (10.5% of the global population) in 2021. If nothing is attempted to remedy the situation, it is estimated that 643 million people (11.3% of the world population) will develop diabetes by 2030 (IDF Diabetes Atlas, 10th edition, 2021) (1).

Diabetes complications are assumed to be produced by vascular and metabolic implications. Among these are cardiovascular disease, stroke, peripheral artery disease, nephropathy, retinopathy, neuropathy, dental disease, and a weakened immune system. These health problems are expected to become increasingly pervasive, affecting both the local and global burden of illness [3]. Diabetes is a systemic disease as it affects various body systems to some extent. For instance, diabetes can disrupt proper cardiovascular, gastrointestinal, immune, and nervous functions. The functional impairment of the peripheral nervous system can lead to diabetic foot and, in worst cases, amputation and hence physical disability. The involvement of retina diabetic retinopathy (DR) can lead to loss of vision and blindness. While in the brain, cognitive dysfunction, with its wide range, from mild cognitive impairment (MCI) to dementia, is also one of the chronic complications of diabetes mellitus [10].

There is an increased risk of diabetes patients could suffer from cognitive decline and dementia (2) which is a form of cognitive impairment. This has major implications for patient care, particularly in older adults with dementia or pre-dementia with cognitive impairment, which are the most typical manifestations in communities worldwide (2). The stages of diabetes associated with cognitive decline depend on the type of diabetes and also the age factor. For type 1 diabetes (T1DM), the impairment of

cognitive function progresses over age. However, for type 2 diabetes (T2DM), there are three stages of a diabetic's cognitive functioning loss, including diabetes-associated cognitive decline, moderate cognitive impairment (MCI), and at the end stage, dementia will occur (3).

Several investigations have revealed that T1DM suffers from severe impairments in information processing, psychomotor efficiency, attention, visuoconstruction, and mental flexibility (4). However, T2DM is significantly more affected by executive function, psychomotor speed, and memory. As a result, older diabetic patients have lower walking pace, poorer coordination, a higher chance of falling, and more fractures, which lowers their quality of life. In addition, executive dysfunction has been linked to the incapacity to carry out their daily tasks.

Diabetes' effects on brain function and cognitive decline have received little attention for a long time. However, a brain magnetic resonance spectroscopy study on diabetic patients' brains discovered various metabolic abnormalities criteria for dementia, establishing new links between dementia and diabetes. There were also extremely low levels of N-acetyl aspartate (NAA), which affects neuronal integrity, high levels of myoinositol, high levels of excitatory neurotransmitters such as glutamate and glycine, and low levels of inhibitory neurotransmitters such as GABA, which has been linked to pain perception problems in diabetic patients (5). Diabetes also causes brain atrophy, myelin degradation, and vacuole dispersion throughout the white matter of the brain in rats (6). Diabetes patients are thought to have irregularities in the metabolism of neurotransmitters in the brain, which leads to neuronal dysfunction and destruction, eventually leading to dementia.

The insulin action research focuses on peripheral diseases rather than brain function (7). Insulin, on the other hand, has been proven to play a role in cognition and neuroprotection in brain. Insulin has an indirect effect on the brain function by acting on peripheral tissues. All circulating variables that change as a result of obesity and diabetes can pass across the blood-brain barrier (BBB) and cause dysfunction in neurons, astrocytes, and microglia [6]. The mechanism of diabetes-induced cognitive

decline is still uncertain. This illness shares cellular and molecular pathways with Alzheimer's disease (AD), the most common form of dementia. (8). Thus, this review describes the factors and putative pathophysiology of diabetes causing cognitive decline, diabetic animal models used to study the condition, and discusses the obstacles and future directions for elucidating the mechanism of diabetes causing cognitive decline.

2. Factors and Pathophysiology of diabetes induces a cognitive decline

Figure 1 shown the factors that contributed to the development of diabetes induced cognitive decline.

2.1 Macrovascular and microvascular diseases

A number of vascular, metabolic, and psychosocial factors have been linked to diabetic-induced cognitive decline. Vascular disease, such as hypertension and dyslipidemia, has been linked to an increased risk of stroke, which is 115% higher in diabetic patients for every 1% increase in HbA1c (9). Furthermore, vascular structure impairments in the brain (cerebrovascular) and heart (cardiovascular) can lead to cognitive decline and dementia. Patients with T1DM who frequently have cognitive difficulties may have both subclinical and overt cerebrovascular disease (10). T2DM patients with elevated plasma triglyceride and higher cholesterol levels have been linked to poor cognitive function (11). Studies have also revealed a relationship between T2DM patients' hypertension and lower cognitive function [5, **6]**. However, due to inconsistent findings from observational studies in the general population [7, **8]**, the role of dyslipidemia and hypertension in the development of cognitive decline in diabetics is still uncertain and needs further investigation.

Microvascular dysfunction also has been connected with the occurrence of cognitive decline (10,16). Chronic hyperglycemia increases the risk of microvascular dysfunction, which affects many organs, including the eye (retinopathy), kidney (nephropathy), and nerves (neuropathy). There is a significant positive correlation between the development of cognitive decline and the presence of nephropathy and/or retinopathy, according to Mukherjee *et al*(2017) [17]. Retinopathy has been linked to

cognitive decline in adult diabetic patients in terms of intelligence, attention/concentration, and information processing (18).

2.2 Hyperglycemia

Hyperglycemia, or persistently elevated blood glucose levels, has been linked to cognitive decline (19). It can affect cognitive function in the long term and also in a shorter period of time. In a shorter period of time, hyperglycemia was associated with impaired working memory, attention, and depression. Acute variations in blood glucose have a negative effect on cognitive performance, and glycemic control improvement is advantageous for regulating. It does not involve structural changes in the microvascular but is mainly due to changes in regional cerebral blood flow or osmotic shifts across the neuronal membrane (20). In contrast, chronic hyperglycemia affects cognitive function through the production of advanced glycosylation end-product (AGE), formation of senile plaques and neurofibrillary tangles, and cerebral microvascular disease that could cause neuronal ischemia and dysfunction in the brain (21). A reduction in white matter volume in the brain has also been connected to diminished executive function and a reduction in the processing of information (22).

The negative impact of hyperglycemia on cognitive impairment was validated in a zebrafish study in which T1DM was imitated by the injection of streptozocin (STZ) [23]. It was discovered in that study that exposing zebrafish to water-diluted glucose for 14 days caused a sustained memory impairment, which was accompanied by an increase in acetylcholinesterase activity. On the other hand, galantamine therapy reversed the memory-damaging effects of hyperglycemia. These findings revealed a link between acetylcholinesterase activity and cognitive impairment in T1DM patients [23].

However, cross-sectional studies on the association of chronic hyperglycemia through HbA1c as a marker and cognitive decline in people with T2DM have yielded inconclusive results [12, **13]**. The association between chronic hyperglycemia and cognitive decline only became apparent in older patients because of improvement in glycemic control through various therapies (26). A study has shown that the treatment of T2DM with either rosiglitazone or glibenclamide (glyburide) improved working

memory over 24 wk (20). Metformin treatment has been shown to reduce the risk of cognitive impairment in diabetic patients (27), but it may also increase the risk (28) or have no effect (29). Treatment with metformin may reduce tau phosphorylation as well as interleukin-1ß-mediated activation of the phosphokinases Akt and mitogen-activated protein kinase (MAPK). Furthermore, it can inhibit the mitochondrial respiratory chain, increasing cyclic adenosine monophosphate (cAMP) and activating protein kinase A (PKA) and AMP-activated protein kinase (AMPK) (30). AMPK activation improved memory and learning in female animal models (31). However, when the evidence from observational studies and randomized control trials (RCTs) is combined, it is to conclude that hyperglycemia and glucose excursions are both weakly associated with poorer cognitive function in people with T2DM (32). As a result, more research into hyperglycemia as a potentially modifiable cognitive risk factor is required.

2.3 Hypoglycaemic

The presence of hypoglycaemic episodes in diabetic patients has also been linked to cognitive decline and an increased risk of dementia [21, **22]**. The human brain, which accounts for 20% of the body's metabolic consumption, has a greater need for glucose as a fuel source. As a result, if our brain is temporarily depleted of glucose, cognitive and emotional functions are impaired. If left untreated, neuroglycopenia can lead to coma, seizures, and brain damage. There is evidence that repeated severe hypoglycaemia in patients with early-onset diabetes can contribute to slower mental development and lower intellectual quotient (IQ) (35). However, the cerebral effects of severe hypoglycemia in adults are still unknown. According to studies, diabetic adults who were insulin-dependent and had experienced repeated severe hypoglycaemia performed worse on neuropsychological tests than diabetic patients who had never experienced severe hypoglycaemia [24, **25]**. Another study found a weak link between the reported frequency of severe hypoglycemia and IQ decrement, lower levels of current IQ, and slowed variable reaction time (38). However, the study has found no cognitive differences between diabetic patients receiving intensive insulin therapy and experiencing severe hypoglycemia and those receiving conventional therapy (39). The

impact of several episodes of severe hypoglycemia between 5 and 15 years is considered mild among young adults dependent on insulin therapy. Strict glycemic control is thought to have a significant benefit in reducing target organ damage and slowing the progression of nephropathy, retinopathy, and neuropathy, but it also increases the occurrence of severe hypoglycemia. As a result, more research on hypoglycemia and cognitive decline is needed to assist diabetic patients in making the best treatment decision.

2.4 Hyperinsulinemia

Hyperinsulinemia caused by endogenous insulin hypersecretion is common in the early stages of T2DM as a result of insulin resistance. According to studies, hyperinsulinemia in adults without diabetes is associated with poorer cognitive function [30, 31, **32]** and an increased risk of AD (43). When compared to normal patients, patients with moderate to severe AD had higher levels of plasma insulin (hyperinsulinemia) but lower concentrations of insulin in cerebrospinal fluid (44). Insulin therapy, both intravenous and intranasal, has been shown to improve cognitive function in AD patients (45). When insulin is injected into the cerebral ventricles of rats, it has been shown to improve memory function. It demonstrated that a similar insulin signaling defect found in peripheral tissues due to insulin resistance could also occur in the insulin receptor in the hippocampus, resulting in functional insulin deficiency and cognitive decline (46). Rosiglitazone (T2DM treatment) can prevent disruption in memory tasks and reduce b-amyloid protein in the brain in transgenic mice that overexpress human amyloid precursor protein and develop AD pathology [37, **38]**. However, more research is needed to determine the link between hyperinsulinemia and cognitive decline.

2.5 Peripheral and cerebral Insulin resistance

Insulin is released into the circulation by the pancreas and can pass the BBB *via* a carrier-facilitated process. The BBB is made up of ependymal cells and brain endothelial cells (BECs), and the blood-cerebral spinal fluid (CSF) barrier has insulin-binding sites

that allow insulin to pass through [6]. The insulin receptor is found in the hypothalamus, prefrontal cortex, and hippocampus, among other places in the central nervous system [8]. The activation of hippocampal insulin receptors is thought to be responsible for insulin-induced cognitive improvement in healthy mammalian brains by facilitating long-term hippocampal potential (LTP), which is linked to learning and memory, as well as increasing the expression of N-Methyl-D-Aspartate (NMDA) receptor [9]. Insulin also regulates the production of neurotransmitters involved in learning and memory, including acetylcholine, norepinephrine, and adrenaline [10], and stimulates the accumulation of GABA A receptors on the post-synaptic membrane [11]. A transient surge in peripheral insulin is thought to cause an increase in CNS insulin, which reaches the brain.

In the healthy stage, insulin binds to the insulin receptor α-subunits and stimulates the tyrosine kinase domain of the β-subunits, resulting in autophosphorylation. This autophosphorylation has the potential to activate the phosphoinositide 3-kinase (PI3K)-Akt (also known as PKB) signaling pathway. Akt molecules (Akt1, Akt2, and Akt3) are serine/threonine kinases that are activated by PI3K in response to growth factors and other cellular stimuli. In the brain, Akt mediates the translocation of glucose transporter type 4 (GLUT 4; also known as SLC2A4) to the plasma membrane. Akt also phosphorylates and inactivates the forkhead box O (FOXO) transcription factor family and glycogen synthase kinase 3β (GSK3β), reducing GSK3β's ability to phosphorylate the microtubule-associated protein tau.

Chronic peripheral hyperinsulinemia induced by diabetes, obesity, or hyperlipidemia produces peripheral insulin resistance (IR) associated with the brain's functional and structural changes. It also contributes to the dysregulation of insulin signaling in the brain and the development of cerebral insulin resistance (IR). Cerebral IR causes insulin transporters at the BBB to downregulate, limiting the amount of insulin that can enter the brain, decreasing the expression and/or activity of insulin receptors, and modulating the phosphorylation state of insulin receptor substrates such as Akt [6]. T2DM patients have lower Akt activation in their adipocytes and skeletal

muscle, leading to many damaging effects on neuronal and glial cells (49). Lower Akt activation affects several downstream components in the insulin signaling cascade, including GSK3β, which regulates the phosphorylation state of the microtubule protein tau and FOXO family of the transcription factor. As a result, it will impair the trafficking of GLUT4 to the plasma membrane of the brain. In addition, memory problems diminish neuroprotective effects, and synaptic transmission may result from this cerebral IR, which may also contribute to the development of neurodegenerative illness [12]. However, the mechanisms underlying the relationships between systemic metabolic and vascular consequences of peripheral IR and cerebral IR are still largely undefined. Observational studies in humans are unlikely to fully elucidate the complex interplay between local and systemic factors of IR in the peripheral and cerebral in the mechanism of diabetes-induced cognitive decline [50, **51]**. Figure 2 shown the insulin receptor signalling in the hippocampus.

2.6 Mitochondrial dysfunction

Mitochondria are involved in oxidative respiration, energy metabolism, free radical production, and apoptosis, among other physiological processes (52). The brain is one of the organs in our bodies with a high energy requirement, and it is particularly sensitive to mitochondrial dysfunction. Mitochondria play an important function in anti-aging and neurodegenerative disease prevention (53). The pathogenesis of diabetes and many neurodegenerative diseases includes mitochondrial dysfunction, which produces reactive oxygen species (ROS) as a by-product that can damage proteins, carbohydrates, and lipids. Mitochondrial dysfunction is less effective in creating ATP but is highly efficient in producing ROS, which is the primary source of the oxidative imbalance seen in cognitive decline (54).

A study has reported that hyperglycemia conditions in diabetes enhance mitochondrial oxidative stress and ROS generation, which can lead to calcium homeostasis disruption, apoptosis, and memory impairment (54). Diabetic rats also had higher levels of superoxide, protein oxidation, and Thiobarbituric acid reactive substances (TBARS) generation (55) and reduced activities of catalase, superoxide

dismutase, and glutathione peroxidase in the brain (56). Excessive oxidative stress causes cytochrome C to be released, and starts the apoptotic cascade and mitochondrial dysfunction (53). These data imply that oxidative stress and its oxidation products are prevalent in diabetes, resulting in an imbalance between oxidative and antioxidant capabilities. It suggests that diabetes may worsen mitochondrial dysfunction and oxidative stress in memory and cognition-related brain regions and may be the fundamental cause of the diabetes-related cognitive decline.

2.7 Neuroinflammation in the Brain

Diabetes raises the levels of pro-inflammatory cytokines in the brain, which can lead to neuronal damage (57). Besides that, vascular endothelial dysfunction also elevates inflammatory mediators and compromises the BBB. When the BBB is broken, neurotoxic blood proteins such as thrombin, fibrin, plasmin, and hemoglobins can potentially enter the brain parenchyma, causing abnormal neuronal activity(58). The pro-inflammatory NF-KB has been implicated in diabetic cognitive decline. According to a study, a pharmacological inhibitor that inhibits NF-KB activation reduces the levels of interleukin-6 (IL-6) and tumor necrosis factor (TNF) and improves cognitive decline (59).

A post-mortem examination of a diabetic patient's hippocampus revealed microglia activity similar to that seen in AD patients [21]. TNF levels and microglial activation in the brain were found to be higher in mice fed a high-fat diet. It was also claimed that diabetes and obesity cause decreased spatial recognition memory in (db/db) mice, which is linked to increased levels of pro-inflammatory cytokines, establishing a relationship between inflammation and cognitive loss [22]. In addition, there is a relationship between neuroinflammation and ROS in cognitive impairment. The creation of ROS in the diabetic brain stimulates a number of cellular pathways, including the advanced glycation end products and its receptor (AGE/RAGE), polyol, and protein kinase C (PKC) pathways, leading to increased brain inflammation and neurodegeneration(58).

2.8 Increase in advanced glycation end products (AGE)

Hyperglycemia in diabetes damage the tissues and increases glucose in the cell. This condition triggers the mitochondria to overproduce reactive oxygen and nitrogen species (RONS) such as superoxide anion radical, peroxynitrite, and hydrogen peroxide (60). RONS, in turn, cause DNA damage and overstimulate peroxisome proliferator-activated receptor (PPAR), a repair enzyme that increases NAD consumption while decreasing the activity of glyceraldehyde 3-phosphate dehydrogenase (GAPDH), which is already compromised by RONS (61). As a result, endothelial dysregulation occurs, as does the initiation of pro-apoptotic signals, such as the production of AGEs products. When AGEs interact with specific receptors (RAGEs), a complex pro-inflammatory cascade involving IL-1, IL-6, TNF, TGF, and VCAM-1 is activated, increasing oxidative stress (60–62). AGE formation alters the structural and functional properties of proteins in both the extracellular matrix and the intracellular region.

2.9 Effect of drugs used in the treatment of diabetes

When compared to untreated patients, diabetic patients who take medication have less improperly aggregated protein and less vascular damage [63, 64]. Metformin, an insulin sensitizer, can reduce the risk of dementia and the rate of cognitive decline in diabetics (63). Biguanides and sulfonylureas, among other diabetes medications, can alter the relationship between tau pathology and diabetes, slowing the onset of cognitive decline (64).

The best way to delay the onset of dementia is to improve early cognitive decline prevention. Not only the elderly but also middle-aged people with diabetes have poorer cognitive functioning and faster cognitive deterioration (65). A retrospective study found that the association between DM and Alzheimer's disease is stronger in middle-aged people than in elderly people, implying that age is a significant factor in the relationship between DM and Alzheimer's disease. Regardless of age, there are usually subjects who develop diabetes but are not actively treated.

2.10 Diabetic Autonomic Dysfunction and Cognitive Impairment

Diabetes autonomic dysfunction (DAD) is a complication of diabetes with unexplained and undiscovered pathogenesis. DAD is related to poor blood pressure regulation and a higher risk of stroke, both of which are risk factors for cognitive impairment. (66). Cognitive decline and autonomic dysfunction have comparable fundamental pathologic mechanisms. The autonomic function is compromised in patients with MCI, Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, and Parkinson's disease with dementia. In comparison to age-matched controls with normal cognition, there is evidence of sympathetic cardiac autonomic dysfunction in patients with MCI [24]. The correlation between blood pressure dysregulation, silent cerebral infarcts, and cognitive decline reveals that intermittent chronic declines in cerebral blood flow caused by high blood pressure can lead to cognitive decline. This process, however, is still unknown and requires additional investigation.

3. Diabetes-induced cognitive decline animal model

3.1 Zucker Diabetic Fatty Rat

Zucker diabetic fatty (ZDF) rats are a genetically derived Zucker fatty strain model of pathological alterations associated with T2DM. Obese ZDF rats have T2DM symptoms such as increased insulin levels, obesity, and triglyceride levels. Genetically, the ZDF rat strain model has also been reported to have abnormally low brain insulin content (67). Studies have found that this model affected memory tests and hippocampal-dependent learning due to hyperinsulinemia [68, **69]**. It is believed that leptin receptor deficiency in the hippocampus of ZDF rats impair the Long-Term Potential (LTP) in the CA1 region and affects spatial memory (70). Another study found that ZDF rats' brains produced more ROS and nitric oxide (NO), as well as complications of redox homeostasis, mitochondrial function, and ATP synthesis (71). Astrogliosis was discovered in the hippocampus, frontal and parietal cortex, and there was an increase in the number of Glial Fibrillary Acidic Protein (GFAP) immunoreactive astrocytes in ZDF rats (72). ZDF rats also exhibit reduced hypothalamic Corticotrophin Releasing Factor (CRF) tone due to dysregulation of the

hypothalamic-pituitary adrenal (HPA) axis that mediates glucocorticoid feedback regulation (73).

3.2 db/db Mouse

The db/db mice are now being used to generate diabetes in rodents in order to better understand the underlying mechanism and aetiology of T2DM. This model includes a leptin receptor gene mutation that causes hepatic insulin resistance, hyperglycemia, hyperinsulinemia, hyperlipidemia, and obesity [28]. The Morris water-maze (MWM) test reveals impaired spatial memory in these mice due to weakness in their leptin receptors in the hippocampus (70). The interaction between cytokines and central processes involving the hippocampus contributes to cognitive behavioral alteration in this db/db mice (74). Reportedly, changes in hippocampal plasticity and function in db/db mice can be reversed when normal physiological levels of corticosterone are maintained, indicating that cognitive impairment in this model may be caused by glucocorticoid-mediated deficits in neurogenesis and synaptic plasticity [75].

The released cytokines, such as IL-1, due to obesity and diabetes in this model can also mediate the neuroinflammation process and impair hippocampal synaptic plasticity (75). The debilitation of memory and learning process in db/db mice due to metabolic changes has the ability to reduced membrane metabolism and tricarboxylic cycle and also restrain the cycle of Gln-Glu/GABA, impartially triggering a rise in anaerobic glycolysis (76). Similarly, Yermakov *et al* (2019) [78], who observed a study on the db/db model in the MWM test's reversal phase, confirmed that it would impact cognitive flexibility. Another study using this model was executed to examine the importance of neutrophils in the db/db mice model after exposure to hypoxic/ischemic (H/I) insult, which might generate higher morbidity and acute ischemic stroke (77).

3.3 ob/ob Mice

The ob/ob mice are a naturally occurring genetic model in which a mutation in the leptin gene causes leptin insufficiency. As a result, they have large appetites to develop obesity and are assigned as an appropriate model for T2DM. A study has been done in ob/ob mice to identify the effect of T2DM disease on tau phosphorylation. This concluded tau hyperphosphorylation for the most part, affected thermoregulation by hypothermia in ob/ ob mice (78). The ob/ob mice with leptin-deficient showed an increment in LTP in the amygdala, indicating that diabetes can have an impact on emotional state (79). A previous study on ob/ob mice showed acute behavioral dysfunction and disability of spatial memory with higher pro-inflammatory cytokines level and NF-κB activation compared to the control (80). A study looked at the lifespan of the ob/ob mouse and found a link between it and the dysregulation of microglia and astrocytes. Higher levels of GFAP and decreased levels of microglial markers followed this finding (81).

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3.4 Goto-Kakizaki Rat

The Goto-Kakizaki rat (GK) was developed from a polygenic non-obese Wistar substrain as a non-obese diabetic animal model for spontaneous T2DM. A study of brain energy metabolism in diabetic GK rats using 13C magnetic resonance spectroscopy found that the glutamate-glutamine cycle between astrocytes and neurons was impaired due to astrocytes having a greater TCA cycle rate than neurons [37]. A study done by Soares *et al* (2019) (83) also proved that diminished brain glycogen metabolism could interfere with memory and learning capability in the GK rat model. The present findings resulted in the successful induction of aging as one of the characteristics of Alzheimer's disease in advance-aged GK rats by increasing phosphorylation of p-Tau level. Furthermore, there was an increment in amyloid-beta (Aβ) level along with a reduction in synaptic proteins in GK rats (84).

3.5 High-fat diet (HFD) rats and streptozotocin injection

In comparison to the regular diet of rats, a high-fat diet (HFD) is likely a diet with a high-fat content mixed with fructose or glucose. According to one study, C57BI/6 mice fed a high-fat lard diet (HFL) increased their body weight and had impaired cognitive function due to increased brain inflammation and decreased BDNF levels (85). Rats fed high-calorie diets such as HFD, high glucose, and fructose diets demonstrated changes in energy and lipid metabolism similar to clinical diabetes, including elevated blood glucose, cholesterol, and triglycerides. This high-calorie diet also decreased spatial learning ability, hippocampal dendritic spine density, and LTP at Schaffer collateral-CA1 synapses. These changes occurred in tandem with a decrease in BDNF levels in the hippocampus [88, 89, **90]**. This effect has also been proposed due to increased corticosterone and peripheral IR, which may contribute to cerebral IR and increase oxidative stress reaction in the brain [91, **92]**.

Many studies have found that rats fed an HFD paired with low-dose Streptozotocin (STZ) also developed obesity and cerebral IR, two key hallmarks of T2DM [41, 40]. The T2DM rat model closely resembled the natural history of disease events to induce insulin resistance, impair beta-cell malfunction and metabolic characteristics of T2DM. STZ is an anti-neoplastic and antibiotic drug isolated initially from *Streptomyces achromogenes* in 1960 and consists of a nitrosourea moiety that is interposed between a methyl group and glucosamine. Due to its severe toxicity to mammalian pancreatic beta cells (insulin-producing cells), it is commonly used in research to generate experimental animal models of T1DM and AD. Its diabetogenic effects are manifested as hypoinsulinemia, hyperglycemia, polydipsia, and polyurea in animals, all of which are characteristic features of diabetes in humans. Although high-dose STZ causes severe impairment in insulin secretion, comparable to T1DM, low-dose STZ has been shown to cause a modest impairment in insulin secretion, which is similar to the feature of T2DM in its later stages [40]. This model would also be easily available, cheaper, and valuable for future research.

4.0 Challenge and Future direction

The role of insulin in the brain, particularly the hippocampal region, has been demonstrated to be critical for functional and structural changes in the brain for cognitive processes. Insulin plays a trophic role in the brain and serves as a metabolic homeostasis regulator, promoting neuroplasticity and high energy regulation. Understanding the molecular mechanisms of insulin on brain plasticity is critical for identifying the mechanisms that regulate neural plasticity in health and metabolic disease, such as diabetes-induced cognitive decline, as well as neurodegenerative disease, particularly AD (91).

To date, research has confirmed the hypothesis that boosting hippocampal insulin receptor signaling could reverse or ameliorate IR-induced neuroplasticity deficits in animal models of T2DM (49). Previous research has also shown that pharmacological and lifestyle interventions can effectively restore hippocampal neuroplasticity in a T2DM animal model (92). A number of studies study also looking into the efficacy of intranasal insulin administration as an innovative therapeutic strategy to alleviate cognitive decline in T2DM, as it allows insulin to be delivered directly to the CNS and avoids systemic hormone effects (45, **93)**. Nonetheless, the findings of all of these studies raise important questions about the localization of intervention strategies' effects, whether they are mediated peripherally or centrally.

The diabetic animal model, which has been used to replicate human cognitive decline, has some limitations and is unreliable in determining the exact human brain condition in diabetes. In addition, diabetes-related cognitive decline has a convoluted etiology, with several variables, such as insulin resistance and insufficiency, as well as pancreatic cell malfunction, all leading to multiorgan deficits. Thus, additional new characteristics of animal models, along with clinical evidence, should be empowered.

As in T1DM, the induction of STZ is involved in pharmacologic toxicity by destructing β cells, which is carcinogenic (94). The challenge of the STZ-induced animal model involves higher mortality of rats due to toxicity is a stumbling block in research.

As the toxicity of STZ can impact multiple organs, it can resemble a contribution to death instead of diabetic complications (95).

Regarding the development of T2DM animal models, potential systemic consequences of disrupted leptin signaling in ob/ob mice to exhibit diabetic peripheral neuropathy should be contemplated (96). Ob/ob and db/mice are assigned as an appropriate model for neuropathy diabetes, exhibiting early onset and approximate nature of neuropathy. However, numerous studies have shown that these models can result in infertility. Furthermore, they could not perpetuate hyperglycemia levels that are inconsistent with the reduction in fasting blood glucose started at the age of 4 wk (97).

HFD rat models can be suggested for future investigations that imitate human conditions. Nevertheless, the abundant diet composition may aggravate interstudy data. To better understand the pathogenesis and therapeutic approaches employing animal models, standardization of induction methods and extensive phenotyping should be prioritized.

Furthermore, the HFD and STZ injection models are more expensive and require a long time to develop. However, animal experimental models that carry significant heterogeneity of diabetes pathology across a broad spectrum of phenotypes seen in patients with cognitive decline must be developed and improved in order to make progress in investigating the causative mechanisms of cognitive decline in diabetes, particularly T2DM.

CONCLUSION

Diabetes-induced cognitive decline can be derived from brain insulin resistance which has been triggered by fluctuation in glycaemic status, macrovascular and microvascular diseases, occurance of neuroinflammation in the brain, mitochondrial dysfunction, increase in the AGE products, and also due to the effect of drugs used in the treatment of diabetes that has been discussed in this review. Furthermore, diabetic autonomic dysfunction also can be linked to cognitive decline,

but the mechanism is still unknown. The pathophysiology of diabetes-induced cognitive decline had a similar mechanism to AD, which is development of brain insulin resistance especially in hippocampus region that affected their neuroplasticity during cognitive processing. However this interplay between diabetes induced cognitive decline and AD mechanism still not completely understood and warrants more inquiry. Understanding the association between diabetes and cognitive decline will provide a better understanding of pathogenesis and cognitive decline in humans, which may assist future researchers in developing potential interventions to alleviate the resulting symptoms of this disease.

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