IBRO Neuroscience Reports 14 (2023) 57–63

Contents lists available at ScienceDirect

IBRO Neuroscience Reports

journal homepage: www.sciencedirect.com/journal/IBRO-Neuroscience-Reports

Review article

Molecular mechanisms underlying hyperglycemia associated cognitive decline

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ARTICLE INFO

Keywords:
Type 2 diabetes
Cognitive decline
Hippocampus
Neuroinflammation
Apoptosis

ABSTRACT

Diabetes mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia. DM can lead to a number of secondary complications affecting multiple organs in the body including the eyes, kidney, heart, and brain. The most common effect of hyperglycemia on the brain is cognitive decline. It has been estimated that 20–70% of people with DM have cognitive deficits. High blood sugar affects key brain areas involved in learning, memory, and spatial navigation, and the structural complexity of the brain has made it prone to a variety of pathological disorders, including T2DM. Studies have reported that cognitive decline can occur in people with diabetes, which could go undetected for several years. Moreover, studies on brain imaging suggest extensive effects on different brain regions in patients with T2D. It remains unclear whether diabetes-associated cognitive decline is a consequence of hyperglycemia or a complication that co-occurs with T2D. The exact mechanism underlying cognitive impairment in diabetes is complex; however, impaired glucose metabolism and abnormal insulin function are thought to play important roles. In this review, we have tried to summarize the effect of hyperglycemia on the brain structure and functions, along with the potential mechanisms underlying T2DM-associated cognitive decline.

Introduction

Diabetes is a metabolic disorder characterized by defects in the body's ability to regulate glucose and insulin homeostasis. According to the International Diabetes Federation (IDF), type-2 diabetes mellitus (T2DM) accounts for atleast 90% of all cases of diabetes, affecting approximately 463 million people worldwide. Increased prevalence of obesity due to unhealthy diets, physical inactivity, and increased average life expectancy, has led to an increase in the prevalence of diabetes, and it has been predicted that the number of patients with T2DM will increase to 700 million by 2045 (Federation, 2019). It has been observed that the age of onset of T2DM is also reduced. Moreover, increasing evidence suggests that T2DM is a major contributor of cognitive decline in elderly as well as young individuals (Lalithambika et al., 2019; Rajamani, 2014). Due to increasing prevalence of T2DM and increased life-expectancy, diabetes-associated cognitive dysfunction has become a serious burden on the available health resources. Therefore, a deeper understanding of diabetes-associated cognitive decline will help in developing novel therapeutic options for this condition.

T2DM affects several organs of the body, including the brain. The association between cognitive decline and T2DM is poorly recognized and is sparsely addressed. The exact mechanism underlying cognitive impairment in diabetes is complex; however, impaired glucose metabolism and abnormal insulin function are often associated with cognitive impairment. Studies have shown that hyperglycemia leads to hypertension, dyslipidemia, inflammation, and abnormalities in hypothalamic-pituitary-adrenocortical axis (Rama and Sagar, 2019; Hazari et al., 2015). Moreover, chronic hyperglycemia is toxic to neurons and leads to the formation of advanced glycation end products leading to oxidative damage and neuronal injury. Inflammation and dyslipidemia are the other important factors that can cause neuronal damage leading to cognitive impairment (Naguib et al., 2020).

T2DM is closely linked to poor performance in a variety of cognitive domains as well as brain structural abnormalities (Dove et al., 2021; Mirahmadizadeh et al., 2020). T2DM and its related cognitive impairment can have a significant impact on people of all age's quality of life (Abdellatif et al., 2020; Xia et al., 2020). Diabetic patients have a lower ability to resist against oxidative stress and have increased activation of inflammatory pathways in the cells (Sharma et al., 2020; Srikanth et al., 2020). People are more susceptible to cognitive impairment and

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https://doi.org/10.1016/j.ibneur.2022.12.006
Received 12 September 2022; Accepted 10 December 2022
Available online 13 December 2022

neurodegeneration as a result of increased oxidative stress and inflammation in the body (Yang et al., 2020; Damanik and Yunir, 2021). Arpita et al. conducted a study of 1278 T2DM patients in a south Indian population to assess cognitive impairment and reported a prevalence of 35.8 % (Chakraborty et al., 2021; Subramanian et al., 2021; You et al., 2021). Individuals with diabetes are 1.5 times more likely than those without diabetes to experience cognitive decline and early stages of dementia (Lin et al., 2022).

It has been reported that hyperglycemia increases the risk of damage to blood vessels within the brain. The structural changes observed in the diabetic brain are hippocampal injury, reduction in gray matter density, reduction in white matter microstructure, and atrophy (Fig. 1) (Seaquist, 2010). Furthermore, the mechanisms underlying structural brain abnormalities in T2DM may include endocrine, metabolic, and vascular pathways.

Type-2 diabetes and cognitive decline

Glucose is the primary source of energy for every cell in the body (Howarth et al., 2012; Fioramonti and Pénicaud, 2019). Despite being only two percent of the body weight, the brain utilizes more than twenty percent of daily energy intake (Erbsloh et al., 1958). Since, neuronal cells are continually active in order to regulate important functions required for the body's survival, they require twice as much energy as cells of the body (Harris et al., 2012; Mergenthaler et al., 2013). Neurons are also active during sleep to manage the sleep cycle, in addition to other critical responsibilities. Therefore, a constant supply of glucose is required for normal brain metabolic processes, brain vitality, cerebral signal conduction, cognitive function, neurotransmission, and synaptic plasticity. Despite the fact that the brain is highly dependent on glucose, severe and long-term hyperglycemia can be harmful (Heni et al., 2015).

Diabetes has been shown in a number of studies to have a negative impact on the hippocampus and to promote neuronal death via a variety of mechanisms (Pamidi and BN, 2012). The hippocampus is a part of limbic system that is particularly vulnerable to elevated blood sugar levels and plays a role in memory, as well as emotional, reproductive and adaptive functions (Foghi and Ahmadpour, 2013; Sadeghi et al., 2016). It also helps in the formation of new memories and the association of emotions and senses like fragrance and sound with memories (Squire, 1992; Lewis, 2012). The hippocampus serves as a memory indicator, directing memories to the brain's right region for long-term storage and retrieval (Turgut and Turgut, 2011; Jarrard, 1993).

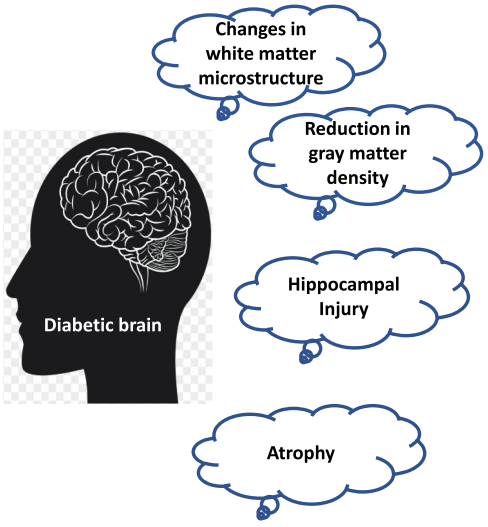

Fig. 1. Structural changes in the diabetic brain. Diabetic patients have a number of structural alterations in the brain and these changes progress with time. These changes include atrophy, changes in white matter microstructure, hippocampal injury, and reduced gray matter density.

Because of its anatomical complexity, the hippocampus is vulnerable to a variety of pathological diseases, including T2DM (Pamidi and BN, 2012; Alvarez et al., 2009; Biessels et al., 1996). The hippocampus's structural complexity has made it prone to a variety of pathological disorders, including T2DM. The granular layer of the dentate gyrus (DG) continues to proliferate throughout life (Kitamura and Inokuchi, 2014; Koehl and Abrous, 2011; Kitabatake et al., 2007). Memory and learning problems can be caused by anything that disrupts the equilibrium between neuronal proliferation and death in the DG region (Van der Borght et al., 2007; Kobilo et al., 2011). Moreover, hyperglycemia suppresses granular cell growth and induces neuronal death (necrosis/apoptosis) in the CA3 region and the DG (Choi et al., 2009; Zhang et al., 2008; Li et al., 2002; Ahmadpour et al., 2010).

Effect of hyperglycemia on the brain structure

Hyperglycemia can cause nerve damage in the brain, increasing the risk of cognitive decline (Sharma et al., 2020; Srikanth et al., 2020; Vieira et al., 2018; Biessels and Whitmer, 2020). Both gray matter and white matter changes are among the T2DM-related brain structural abnormalities (Chen et al., 2021). Patients with T2DM experience cognitive decline and anatomical brain abnormalities, especially observed in the hippocampus (Li et al., 2020). Patients with T2DM exhibit brain shrinkage, as evidenced by reduced total and regional white and gray matter volumes (Moran et al., 2013). Additionally, it was found that T2DM patients had a little larger volume of white matter hyperintensities than non-T2DM patients (Moran et al., 2017). These abnormalities in the brain may serve as imaging biomarkers for T2DM alone or T2DM combined with cognitive decline (Zhang et al., 2011).

People with T2DM exhibit somewhat more global brain atrophy than those without diabetes, and this atrophy steadily worsens over time in comparison to normal ageing. Additionally, vascular lesions, especially lacunar infarcts, are more frequent. Numerous research examined the connection between brain atrophy and diabetes; some only looked at cortical or subcortical shrinkage, while others looked at both (Falvey et al., 2013; SK et al., 2003). Hippocampal atrophy has been suggested to occur in T2DM patients. Atrophy of the medial temporal lobe, in especially the hippocampus, is regarded to be a sign of neurodegeneration (Scheltens et al., 2002; Korf et al., 2007).

Global brain atrophy, which happens gradually over time compared to normal ageing, is slightly more common in adults with T2DM than in people without diabetes (Knopman et al., 2011, 2005). Vascular lesions, especially lacunar infarcts, are also rising in frequency. Numerous investigations examined the relationship between brain atrophy caused by diabetes and cortical or subcortical atrophy, or both (Knopman et al., 2005). According to certain theories, those with T2DM may experience hippocampal atrophy. According to numerous studies, the hippocampus in the medial temporal lobe, in particular, is thought to atrophy as a marker of neurodegeneration (Brundel et al., 2014).

Potential mechanisms underlying hyperglycemia-induced cognitive impairment

Apoptosis

A considerable rise in apoptotic markers including Bcl-2, Bcl-xl, Bax, and caspase 3 has been observed in the hippocampus environment of diabetic mice in several preclinical studies (Li et al., 2002). In the hippocampus of STZ-induced diabetic rats, Jafari et al. reported that Caspases 3 is the most important member of the caspases family, showed a significant increase in activity. In these diabetic rats, Bax expression was dramatically raised at both the mRNA and protein levels, whereas Bcl xL and Bcl 2 expression was significantly reduced, implying that hyperglycemia-induced apoptosis in the hippocampus of diabetic rats could be mediated by mitochondria (Jafari Anarkooli et al., 2014).

Several other in vitro and in vivo investigations have found that diabetic mice suffer from hippocampus cell loss, which could be a vital contributor to memory and learning problems (Fig. 3) (Li et al., 2002).

Oxidative stress

Oxidative stress has been related to the onset and progression of diabetes, as well as the problems that come with it. Hyperglycemia leads to the formation of reactive oxygen species (ROS), other oxidative stress markers and reactive nitrogen species (RNS) (Cheong et al., 2020). Furthermore, hyperglycemia is linked to a reduction in antioxidant levels in the brain (Valko et al., 2007). In diabetic rats, increased oxidative stress has been linked to the development of cognitive deficits (Fukui et al., 2002; Comin et al., 2010).

Circulating microRNAs (miRNAs) can be used as biomarkers of T2D (Zampetaki et al., 2010; Prattichizzo et al., 2016; Kato et al., 2013). miRNAs are a class of non-coding RNAs which interact with the 3′ untranslated region (3′ UTR) of target mRNAs to induce mRNA degradation and translational repression (Bartel, 2009). The two candidate miRNAs (miR-192 and miR-193b) were reported as markers of pre-diabetes by Parrizas et al. in a cohort study (Párrizas et al., 2015). Furthermore, de Candia et al. reported a unique miRNA signature link to prediabetics with respect to disease progression (De Candia et al., 2017).

La Sala et al. demonstrated the association between circulating miR-21 and glycaemic dysfunctions and provided novel and valuable insights into the molecular characterization of impaired glucose tolerance (IGT) status (La Sala et al., 2019). An increase in levels of circulating miR-21 was observed in IGT subjects. In addition, results showed a positive correlation of miR-21 and postprandial glucose levels with ROS and insulin resistance index. It has also been reported that miR-21 could be an important modulator of ROS homeostasis and antioxidant pathways, and defective antioxidant response is one of the major causes of cellular damage (La Sala et al., 2016).

Hyperglycemia is one of the major risk factors of AD (Shieh et al., 2020; Li et al., 2017; An et al., 2018; Jash et al., 2020). High blood glucose levels increase oxidative stress leading to the production of lipid peroxidation byproducts, such as 4-hydroxynonenal (HNE), which lowers the antioxidant defense mechanism in AD patients. AD patients may have increased levels of HNE in the brain and blood, thereby, enhancing the production of Aβ (Arimon et al., 2015; Di Domenico et al., 2017; Liou et al., 2019). Sanotra et al. showed that this could be a result of both HNE adducts and Aβ being neutralized by associated autoantibodies. When HNE adducts and levels of Aβ continue to increase, it may deplete these crucial neutralizing antibodies and promote a cellular environment for neurodegeneration, leading to pathologic states such as AD (Sanotra et al., 2022). Further research on HNE immune responses is needed to get more insight of the pathogenesis from hyperglycemia to AD.

It is well known that hyperglycemia-induced neurotoxicity is mainly due to increased production of advanced glycation end-products (AGEs), increased polyol pathway flux, activation of protein kinase C (PKC) isoforms, and increased hexosamine pathway flux, (Brownlee, 2001) all of which leads to an increase in oxidative damage and vascular complications shown in Fig. 2. Few studies suggest that blood-brain barrier (BBB) permeability is reduced in diabetic animal models due to degeneration of the cerebral vasculature (Prasad et al., 2014; Ueno et al., 2016). However, there is conflicting information about cerebral microcirculation and BBB disruption in diabetic rodent models with chronic hyperglycemia (Weiss et al., 2009; Huber et al., 2006; Rom et al., 2019; Xu et al., 2013).

Nerve cells are particularly susceptible to hyperglycemia because neuronal glucose uptake is highly dependent on external glucose concentration, which is 4–5 times greater in diabetics. It has been shown that the levels of neurotrophic support factors, such as nerve growth factor and insulin-like growth factor, are decreased in diabetic patients, leading to nerve malnourishment. As shown in Fig. 2, all of these pathways function together to provide a platform that leads to neuronal dysfunction and nerve injury in diabetic animals (Sims-Robinson et al., 2010).

Impaired neuronal insulin signaling

Insulin plays an important role in neuroprotection. Insulin activates insulin receptor substrates 1 and 2 by binding to the insulin receptor (IR). IRS1 is generally located in the cerebral cortex, while IRS2 is mostly found in the hypothalamus (Mullins et al., 2017; Arnold et al., 2018). Insulin attaches to IR/IRS and activates a variety of secondary messengers through three main mechanisms:

a. The IR-Shc-MAP kinase (MAPK) pathway is activated, which promotes synaptic plasticity, protein expression for cell growth and maintenance (Yao et al., 2004). Insulin also regulates protein transcription, translation, and post-translational modification via the MAPK pathway (Kelly et al., 2003; Dou et al., 2005).

b. By regulating neuronal transmission via cyclic nucleotide

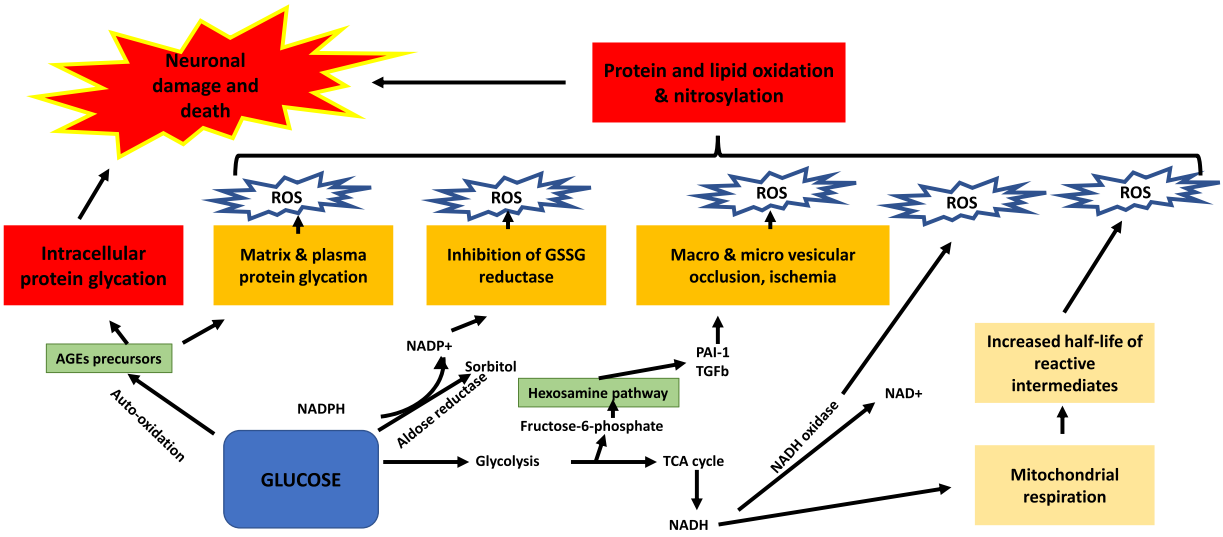

Fig. 2. Mechanisms underlying diabetes-associated cognitive decline. Abnormally high levels of blood glucose can lead to the activation of numerousmetabolic pathways like polyol pathway, advanced glycation end products (AGE) pathway, protein kinase C (PKC) pathway, and hexosamine pathway which in turn leads to neuronal damage.

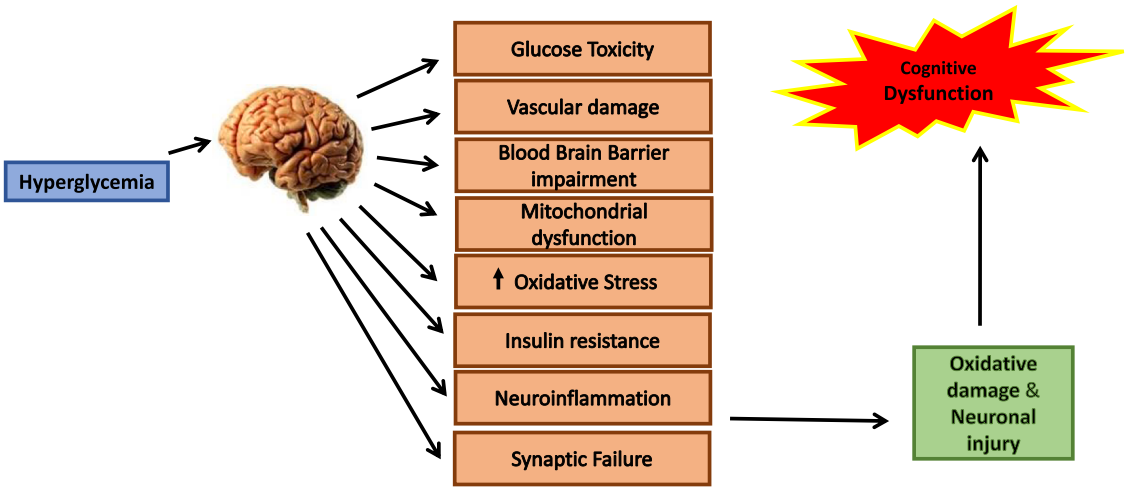

Fig. 3. Pathway through which hyperglycemia leads to cognitive impairment. Hyperglycemia leads vascular damage, BBB impairment, mitochondrial dysfunction, increased oxidative stress, IR, neuroinflammation, synaptic failure resulting in oxidative damage and neuronal injury.

phosphodiesterase 3B, the phosphatidylinositol 3-kinase (PI3K) pathway influences cognitive function, and memory (cPD3B) and information processing. Inhibition of neuronal apoptosis is also linked to the PI3K-Akt pathway (Zhao et al., 2004). Glycogen synthase kinase 3 (GSK3), forkhead box O1 (FOXO1), mammalian target of rapamycin (mTOR) and nuclear factor B (NFkB) are some downstream effectors of PI3K-Akt. Memory and learning are directly influenced by these effectors.

c. Direct activation of NMDA glutamate receptors to increase the opening of calcium channels at synapses to mediate neurotransmission (Wan et al., 1997). Increased calcium uptake promotes NMDA-mediated neurotransmission, which increases the recruitment of functional GABA receptors to postsynaptic sites and enhances GABA transmission, regulating synaptic inhibition for learning and memory tasks (Fig. 4) (Cheong et al., 2020).

Suppressed insulin activity

Despite the fact that the brain is not an insulin-dependent organ, insulin crosses the BBB and binds to receptors on glial cells and neurons. Although it is unknown whether insulin resistance exists in the CNS, emerging research revealed that insulin insensitivity may play a role in the development of obesity and T2DM. Insulin has multiple functions in the brain, and causes increased glucose uptake in the neurons of the hippocampus and frontal lobes, two of the most important regions involved in memory regulation. Insulin also aids in the formation of new memories by increasing synaptic connections between brain cells. Insulin also controls the metabolism and release of acetylcholine, a neurotransmitter that is important for cognition. Finally, insulin plays a role in blood vessel formation (Arnold et al., 2018).

Insulin increases the production of insulin degrading enzymes (IDE) and generates the extracellular release of the β-amyloid peptide (Aβ)

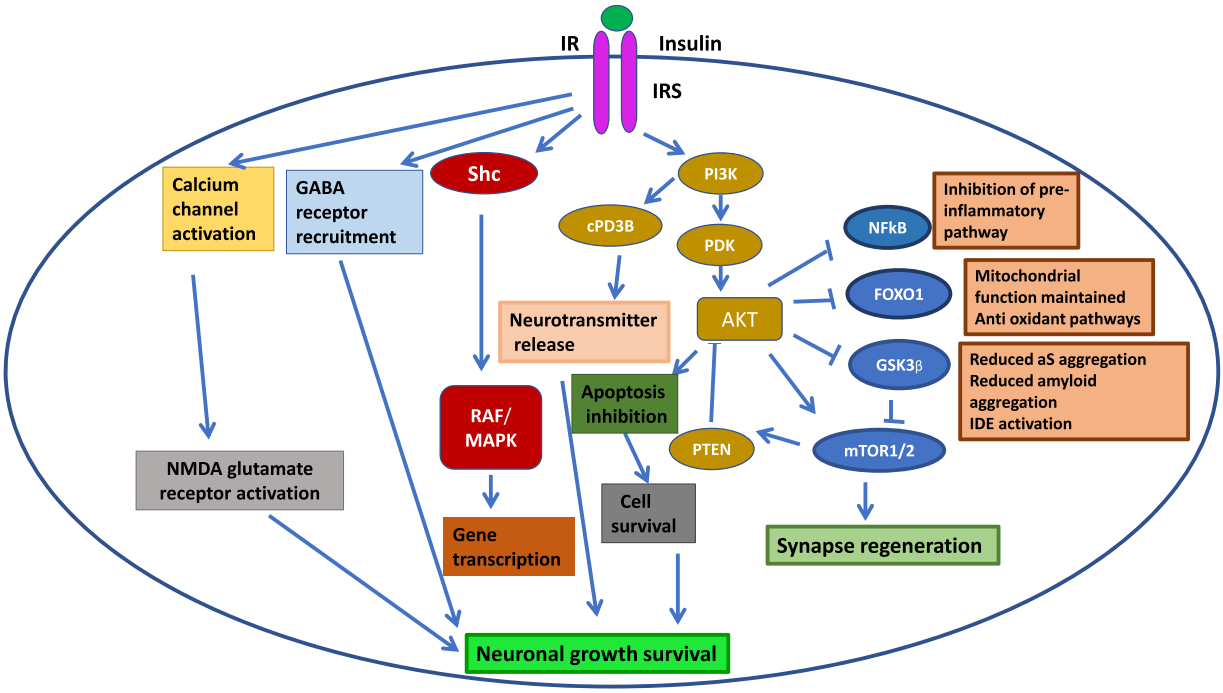

Fig. 4. Insulin signaling pathway. Insulin activates IRS1 and 2 by binding to the IR. Insulin attaches to IR/IRS and activates a variety of secondary messengers through three main mechanisms:PI3K/AKT pathway, MAPK pathway, NMDA glutamate receptor activation pathway.

(Young et al., 2006). Insulin deficiency leads to the buildup of Aβ. There is a reduction in insulin receptors and insulin in the brain when there is hyperinsulinemia or insulin resistance (Kawamura et al., 2012). Because IDE degrades insulin, high insulin levels causes IDE consumption, which leads to an increase in Aβ deposition. As a result of the increased Aβ buildup, cognitive impairment occurs (Biessels et al., 2006; Kodl and Seaquist, 2008; Craft, 2005).

Brain insulin resistance

Insulin resistance is characterized as a decrease in the body's sensitivity to insulin (Goldstein, 2002). Insulin resistance is the inability of brain cells to respond to insulin. Insulin receptor downregulation, insulin receptor inability to bind insulin, or improper insulin signaling cascade activation could all contribute to this lack of responsiveness. At the cellular level, this dysfunction impacts neuroplasticity, receptor modulation, and neurotransmitter synthesis, as well as processes directly engaged in insulin metabolism, such as neuronal glucose absorption in GLUT4-expressing neurons, and insulin homeostatic and inflammatory responses (Mielke et al., 2005).

In the brain, insulin and related proteins are necessary for cell survival. A range of brain processes, including learning and memory, appear to be governed by glucose and insulin. Chronically high or low blood glucose levels can cause brain damage and cognitive impairment by disrupting insulin activity. Insulin insensitivity in our liver, fat, and muscle cells/tissues may also corresponds to insulin sensitivity in our central nervous system (insulin resistance at the level of brain), according to new findings. The regions of the brain involved in cognition, memory, and learning are affected. Insulin plays a role in the cell-level memory formation process known as long-term potentiation. Insulin also regulates acetylcholine, a chemical messenger that plays a role in memory (Arnold et al., 2018; Cholerton et al., 2016).

Neuroinflammation

The expression of pro-inflammatory cytokines in the brain rises in diabetic individuals, resulting in neuronal damage (Gaspar et al., 2016). It's thought that the transcription factor NF-kB is involved in cognitive function. BAY 11–7082 (BAY) is a pharmacological inhibitor of IkB (inhibitor of kappa B alpha) phosphorylation that reduces IL-6 and TNF levels while inhibiting NF-kB activation. BAY improves learning and memory in T2DM rats without compromising glycemic control (Kumar Datusalia and Sunder Sharma, 2016). Furthermore, microglial activity is enhanced in diabetic human postmortem hippocampus, indicating increased inflammation (Valente et al., 2010).

TNF levels and microglia/macrophage activation were found to be higher in the brains of mice on a high-fat diet, indicating pro-inflammatory changes in the brain (Puig et al., 2012). The spatial-recognition memory of diabetic and obese db/db mice was reduced, which was connected to higher levels of pro-inflammatory cytokines (IL-1, TNF, and IL-6), implying a relationship between inflammation and memory impairment (Dinel et al., 2011). The relationship between oxidative stress and neuroinflammation is widely understood. NF-kB is a regulator of TNF and interleukins and a modulator of reactive oxygen species (ROS). It is involved in the commencement of the inflammatory cascade. Increased ROS production and cognitive impairment occur from TNF upregulation, which inhibits insulin signaling (Fig. 5) (Kuhad et al., 2009).

Synaptic dysfunction

Synaptic damage is the most common cause of brain malfunction (Morrison and Baxter, 2012), and the severity of synaptic alterations is related to the severity of cognitive loss (Hawkins and Byrne, 2015). Amyloid plaques are the primary cause of synaptic dysfunction, but neuroinflammation and microglial activation also plays an important role (Moore et al., 2019). Mitochondria plays a role in synaptic degeneration because of a lack of ATP synthesis (energy failure), impaired production of neurotransmitter precursors and metabolites, increased production of reactive oxygen species (ROS), decreased Ca++ handling, dysregulation of mitochondrial dynamics, and mitochondrial dependent cell signaling transduction (Tait and Green, 2012; Guo et al., 2017; Belenguer et al., 2019). The hippocampus, a part of the brain known to play a role in memory formation in animals, is severely compromised by diabetes, and electrophysiological studies show that diabetes decreases synaptic plasticity in hippocampal slices (Biessels et al., 2002; Trudeau et al., 2004; Duarte et al., 2019; Garcia-Serrano and Duarte, 2020).

Conclusion

Brain function is intimately linked to glucose metabolism. T2DM is now widely understood to be linked to poor cognitive performance. Free radicals and reactive oxygen species (ROS) have been identified as the primary drivers of neuronal death in diabetic mice. Studies have

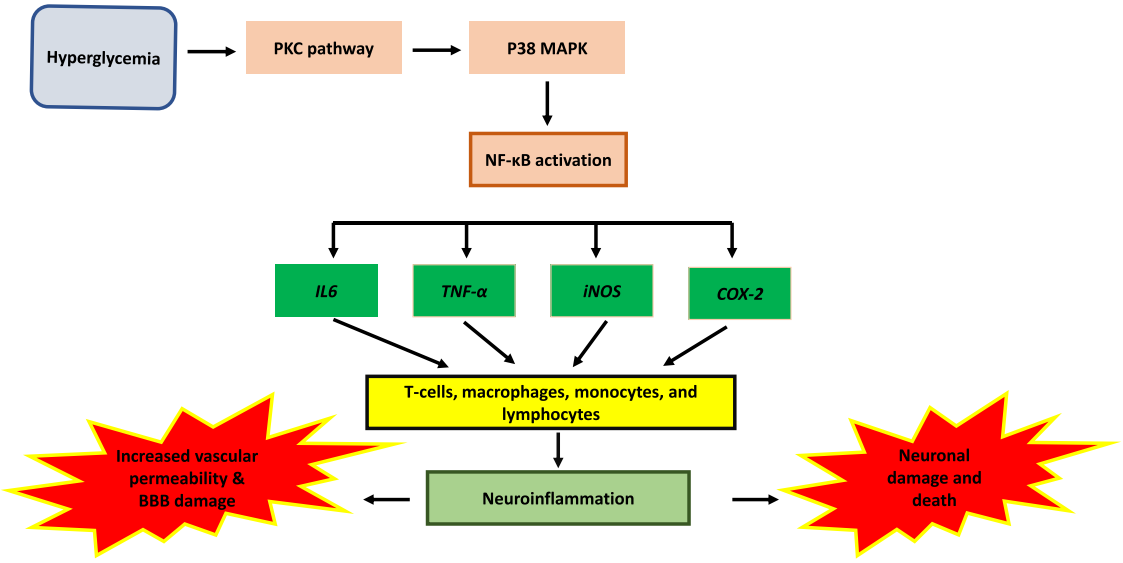

Fig. 5. Hyperglycemia leads to neuroinflammation. Hyperglycemia activates PKC pathway which in turn activates NF-kB pathway leading to neuroinflammation, increased vascular permeability, and BBB damage.

reported that ROS and the resulting oxidative stress play a pivotal role in apoptosis. The information provided in this review demonstrates the overlap between the biological pathways driving diabetes and cognitive impairment. Hyperglycemia causes dysregulation of several extracellular and intracellular signaling cascades in the CNS, resulting in decreased neuronal and synaptic function and, as a result, an increase in neuronal death. An understanding of how each molecular pathway intersects and affects the other is critical for the development of future drug intervention strategies for diabetes-associated cognitive dysfunction.

Funding resource

This review did not receive any specific grant from any of the funding agencies.

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