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Pathogenesis of T2DM-induced cognitive impairment and possible role of PCG1-α /FNCD5/BDNF pathway

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Abstract

Diabetes mellitus is the most common metabolic illness. Type 2 diabetes mellitus (T2DM) accounts for about 537 million people worldwide with prediction of an increase in the future. T2DM has several complications including cardiovascular, renal, and neurological complications. A large growing data demonstrated that T2DM affects negatively the cognitive domains leading to defects in learning and memory loss especially in elderly patients. The pathophysiology of diabetes-induced cognitive deficits includes neuroinflammatory pathways, apoptotic pathways, and defects in proliferator-activated receptor-gamma co-activator 1α / fibronectin type III domains containing protein 5/ Brain-derived neurotrophic factor (PCG1-α /FNCD5/BDNF) signaling. Exercise training and Vitamin D supplementation are hopeful therapy have been recognized to improve cognitive dysfunction due to diabetes mellitus.

Keywords: Hippocampus; BDNF; PCG-1α; FNCD5; Cognitive impairment

Full-length article **Corresponding Author*, e-mail:

1. Introduction

According to an epidemiological study, 537 million people worldwide have diabetes, and as the population ages and individuals live longer, this figure is predicted to rise to over 783 million by 2045[1]. Worldwide, diabetes mellitus is a common metabolic disorder. More than 90% of people with diabetes have type 2 diabetes mellitus (T2DM), which results in micro and macrovascular issues that are extremely distressing for both patients and caregivers [2-3]. T2DM is characterized by insulin resistance in target organs and pancreatic β-cell dysfunction which leads to insulin deficiency (4). Bad dietary habits and a sedentary lifestyle are non-physiological factors that contribute to the development of T2 DM diabetes. Diabetes is a metabolic illness that negatively impacts several brain areas, including the hippocampus, and raises the risk of cognitive decline (5). T2DM leads to many chronic complications, including peripheral neuropathy, diabetic retinopathy, and cardiovascular disease. [4].

2. Impact of diabetes on cognitive function

Diabetes mellitus, both type 1 and type 2, has been linked to decreased cognitive function. Diabetes can cause cognitive abnormalities even in its very early stages. the type and severity of cognitive impairment affected by glycemic control and the duration of diabetes [5]. T2DM patients run the risk of having poor cognitive function brought on by memory loss and executive dysfunction. [6-7].

3. Manifestation of cognitive impairment in the diabetic patient

Type 2 diabetes mellitus is closely linked to structural abnormalities of the brain and decreased performance across many cognitive function domains. With the increasing diabetes epidemic and aging population, neural complications of diabetes are expected to increase and become a future health challenge. Understanding the manifestation of cognitive impairment, pathophysiology and factors associated with this problem is essential for proper dealing with this potentially distressing sequence of T2DM [8]. Learning and memory abilities were specifically assessed in elderly diabetic patients and it was found that diabetic patients performed worse than age-matched non-diabetic comparison subjects. Deficits appear to be most prevalent in list learning tasks when the subject is required

to recall a list of words in any sequence after hearing or seeing them one at a time. In older persons with Type 2 diabetes, memory, or the capacity to recall information minutes or hours after initially being exposed to it, is also affected. Adults with long-term Type 1 diabetes rarely experience problems with their learning or memory [9]. Lower baseline levels of memory, executive functioning, language, processing speed, and visuospatial ability were associated with diabetes mellitus. Although persons with diabetes mellitus have a bad cognitive function, both those with and without this disease exhibit equal rates of cognitive change. These results indicate that cognitive alterations may appear early in the course of diabetes mellitus and stress the need for studies to start following patients at least in midlife, before the typical later-life onset of dementia [10].

4. Pathogenesis of diabetes-induced cognitive impairment

The mechanisms underlying diabetic cognitive impairments are multifactorial, including neuro-inflammatory pathways, apoptotic pathways, and defects in proliferator-activated receptor-gamma co-activator 1α / fibronectin type III domains containing protein 5/ Brain-derived neurotrophic factor (PCG1-α /FNCD5/BDNF) signaling.

4.1. Hippocampus neuroinflammation and apoptosis

One of the areas of the brain most susceptible to metabolic disorders, such as diabetes mellitus, is the hippocampal region. [11]. The left and right hemispheres of the brain each contain an individual hippocampus, which is a paired structure with a horseshoe shape. [12]. A crucial part of the limbic system, the hippocampus is essential for the development of memories as well as emotional, sexual, and adaptive behaviors [12]and also is critical for the formation of new memories, hippocampus structural damage primarily affects recently acquired memories, but previously acquired old memories remain unaltered [13]. Studies have demonstrated that cell proliferation continues in the hippocampus constantly. This unique hippocampal production of neurons in the adult brain is necessary for memory formation [13, 14]. According to epidemiologic studies, the development of inflammatory biomarkers is related to type 2 diabetes mellitus and its complications. Patients with diabetes have elevated serum levels of interleukin-6 (IL-6), C-reactive protein, and tumor necrosis factor-alpha (TNF-alpha) [15]. Hyperglycemia induced damage in the Neurons of the cortical and hippocampal functional areas, which can result in severe spatial learning and memory dysfunction. It has been demonstrated that excessive immune system activation is an important factor in the appearance of T2DM [16]. The nuclear translocation of nuclear factor-kappaB (NF-κB) and its linked death-related proteins, such as cysteinyl aspartate-specific proteases (caspases) and TNF-α may increase brain injury induced by diabetes [17].Inflammatory cytokines including IL-6 and TNF- are persistently increased in patients with metabolic syndrome. surprisingly, higher inflammatory markers were linked to decreased executive function in those with metabolic syndrome[16].

Diabetes mellitus causes oxidative stress through the self-oxidation of glucose, protein glycosylation, and polyol processes free radicals are generated. Persistent cell damage is caused by decreased antioxidant levels and increased amounts of reactive oxygen species [18]. Neuroinflammation in the hippocampus leads to oxidative stress, which in turn, becomes a source of inflammation. In reality, this harmful chain reaction has significantly contributed to diabetes-induced cognitive impairment [19]. It has been found that diabetes-related hippocampus neuronal cell loss may be mediated by apoptosis. According to reports, apoptosis has a role in neurodegenerative diseases like Alzheimer's disease [20, 21]. It's reported that 1 and type 2 diabetes have a hurt impact on dendritic remodeling, diminished hippocampus neurogenesis, and increased apoptosis [22]. Apoptosis is a metabolically active, tightly controlled, genetically encoded, and physically different form of programmed cell death [21].

The extrinsic pathway, also known as the death receptor-mediated pathway or the caspase pathway, and the intrinsic pathway, also known as the Bcl-2 regulated or the mitochondrial pathway which is accompanied by both pro-apoptotic and anti-apoptotic signals, are two separate processes by which apoptosis occurs [23]. Bax is a pro-apoptotic factor and one from the Bcl-2 family member which is a set of cytoplasmic proteins that regulate apoptosis [24, 25]. Bax was first discovered as a protein from various cell lines that co-immunoprecipitated with Bcl-2. Analysis of the Bax protein's amino acid sequence revealed that Bcl-2 and Bax are extremely similar. The cells died by apoptosis at a much higher rate than normal. As a result, Bax was the first Bcl-2 family member to be recognized as an apoptotic promoter [26]. Members of the Bcl-2 family act as crucial mitochondrial pathway regulators of apoptosis. Members of this family include both cell death inducers and inhibitors. The BH1, BH2, BH3, and BH4 conserved homology domains are present in members of the Bcl-2 family. Bax causes cell death by homodimerizing and heterodimerizing with Bcl-2 and other Bcl-2 protein family members [27].

4.2. Role of PGC-1α

The translational co-activator peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) is highly expressed in different oxidative tissues including the brain, skeletal and cardiac muscle, brown adipose tissue, and the kidney (29). The structure of PGC-1α is composed of the N-terminal region (aa1-200), the middle region (aa200-400), and the C-terminal region (aa400-797) [28]. PGC-1α is a transcriptional coactivator that regulates the energy metabolism-related genes and also regulates mitochondrial biogenesis and activates the expression of multiple detoxifying/antioxidant enzymes, so it strongly maintains the equilibrium between the synthesis and scavenging of pro-oxidant chemicals and regulates cell metabolism [29]. Because there are more mitochondria numbers, PGC-1α may convert the white fat appearance and physiology into that of brown fat increasing thermogenesis.

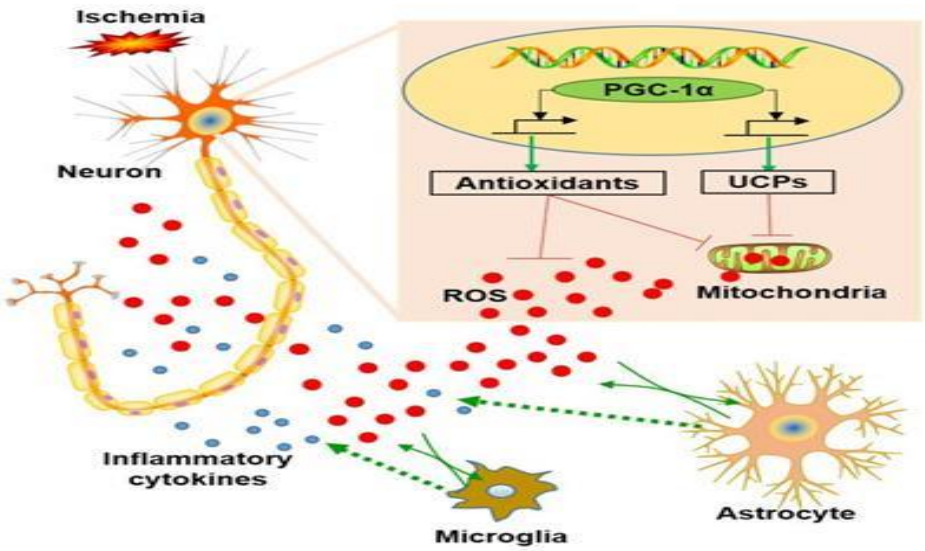

Figure 1: Role of PCG1-α in mitochondrial biogenesis [30]. PGC1-α peroxisome proliferator-activated receptor-γ co-activator 1α, UCPs uncoupling proteins, ROS reactive oxygen species.

In addition, in an animal model, higher PGC-1 expression was observed to prevent systemic chronic inflammation and insulin resistance as well as aging-related sarcopenia and bone loss [30]. Brain PGC-1α is downregulated in the T2 DM rat model [31]. Elevated PGC-1α level in the hippocampus protects neurons from apoptosis by activation of anti-oxidant genes and also promotes the formation and maintenance of synapses[32]. Brain PGC-1α expression is increased in response to physical exercise which acts as a Signal that relays metabolic needs[33].

4.3. Role of FNDC5

FNDC5 (fibronectin type III domains containing protein 5) is a glycosylated type I membrane protein. The proteolytic cleavage of FNDC5 yields irisin, which has 112 amino acids. The FNDC5 gene, which has 6 exons and 5 introns, is found on chromosome 1p35.1 [34]. In both human and animal samples, FNDC5 is found in the heart, liver, skeletal muscle, brain, ovary, kidney, spleen pancreas, lung, prostate, adipose tissue, intestine, and colon[35]. It is known that FNDC5 is highly expressed in the brain's hippocampus, cerebellar Purkinje cells, and hypothalamus, among other areas [34]. Overexpression of FNDC5 in primary cortical neurons enhanced cell survival, but FNDC5 knockdown in neural precursor cells impaired neuronal and astrocyte development and decreased cell survival [36, 37].

PGC-1α regulates neuronal FNDC5 gene expression (35) and Brain derived neurotropic factor (BDNF) expression was elevated in primary cortical neurons by the expression of FNDC5. [38]. Numerous studies demonstrated that exercise can induce adult hippocampal neurogenesis through an increase in both BDNF and FNDC5, helping improve cognitive dysfunction in a mouse model of Alzheimer's disease [39]. A previous study demonstrated that diabetes reduces the mRNA expression of FNDC5 in muscle [40], so further studies are needed to clarify the effect of Type 2 diabetes on the FNDC5 expression in the hippocampus and diabetes induce cognitive impairment.

4.4. Role of BDNF

Brain-derived neurotrophic factor (BDNF) has 27-kDa polypeptide that binds to the unselective p75NGFR receptor and high-affinity protein kinase receptors (Trk). Four promoters that are differently expressed in central or peripheral tissue with multiple regulatory elements make up the structure of the BDNF gene complicated [41]. The human brain's multiple regions, including the hippocampus, the area responsible for learning and memory, express BDNF. BDNF is a member of the neurotrophins' superfamily, plays a crucial role in modulating synaptic transmission in the brain by regulating the maintenance, growth, and survival of neurons in animals and humans since it can protect against neuroinflammation and neuronal degradation[42]. It has been hypothesized that BDNF is an important factor in long-term memory induction and consolidation and persistent strengthening of synapses depending on recent forms of activity[43]. Numerous organs, such as the skeletal muscle, retina, prostate, kidneys, and platelet, express BDNF[44]. Synaptic plasticity means the process by which synapses change in strength regarding an increase or decrease in synaptic transmission, so Synaptic plasticity is considered a functional term. The strength of transmission physiologically changes are often associated with alterations in the structure of the synapses. Because synapses were believed to be the site of storage for brain memories, synaptic plasticity is considered to be the cellular mechanism for learning and memory [43]. According to the findings of Zhen et al. (2013). BDNF may be involved in the pathogenesis of cognitive impairments, particularly delayed memory in T2DM [45] . it was demonstrated that BDNF secretion in the brain is suppressed by hyperglycemia [46]. In another recent research, the overexpression of BDNF in

the hippocampus of the brain prevents neuroinflammation that develops in diabetes' hyperglycemic stress conditions as well as the decline of synaptic plasticity[47].

Diabetes causes the brain to experience significant oxidative stress and hyperglycemia that in diabetic patients activates the advanced glycation end products- receptor for advanced glycation end products (AGE-RAGE) axis, which then induces neuroinflammation, decreases the long-term potentiation, develops vascular dysfunction, and decreases BDNF levels in the brain [48].

5. Possible new therapy

5.1. Exercise and brain function

It is well-recognized that engaging in regular physical activity improves cardiovascular health and lowers the risk of developing metabolic disorders. Additionally, regular exercise has been shown to lower the incidence of dementia and depression. [49]. Light and moderate physical activity, seem to be good for mental function in people with T2 DM. Diabetes is linked to decreased cognitive function scores, especially when poorly controlled, and regular physical activity may prevent some of the cognitive deterioration that could occur [50]. Recently, a 16-week progressive treadmill exercise program was reported to enhance an upregulation in SIRT-1 and PGC-1α [51]. Early on throughout endurance training, Before the expression of PGC-1, PGC-1 is activated leading to mitochondrial biogenesis in the skeletal muscle of humans and also mitochondrial biogenesis enhanced in long-term endurance exercise by stimulating the p38 mitogen-activated protein kinase (MAPK), which activates the PGC-1 transcription factor increasing PGC-1 expression [52]. A conceivable mechanism for how exercise protects neurons and enhances cognitive function is through the induction of neurotrophins such as Brain-derived neurotrophic factor. While it has been suggested that exercise increased cerebral blood flow, oxygen, and nutrient delivery to neurons, as well as clearance of metabolic waste, this is only one possible mechanism. [53]. It was discovered that there is a direct relationship between physical activity and cognitive ability because exercise causes an increase in hippocampal volume, confirming that physical activity can alter the physiological function and anatomical structure of the brain [54].

5.2. Vitamin D and brain function

Traditional knowledge of vitamin D (VD) refers to it as a steroid hormone for calcium metabolism, bone functions, and numerous physiological processes, including inflammation and glucose homeostasis are influenced by vitamin D. The hippocampus, the pancreas, Adipose tissue, and the intestinal barrier epithelium and are just a few of the tissues that have a lot of VD receptors. Because it crosses the blood-brain barrier, it may also play a role in brain activities. It has been demonstrated that the brain contains a large number of the vitamin D receptors and enzymes necessary for its function [56, 57]. Low vitamin D levels have been associated with fractures, different autoimmune diseases, diabetes mellitus, cardiovascular disease, malignancy, falls, and depression [58, 59]. One of the key risk factors for dementia has been identified as vitamin D insufficiency [60]. Alpha-1-hydroxylase activates vitamin D to its activated form in many areas of the central nervous system (CNS), particularly the hippocampus. Through detoxifying processes and the production of neurotrophins, vitamin D3 may safeguard the integrity and structure of neurons [61].

According to prior studies, persons with type 2 diabetes who had lower serum levels of vitamin D have milder cognitive impairment [62]. Vitamin D3 supplementation may have a protective impact on the brains of diabetic animals by improving the cholinergic transmission in the prefrontal cortex [63]. In VD-deficient T2D patients, VD supplementation may ameliorate T2D by lowering HbA1c and raising SIRT1 and irisin [64]. Another study discovered that vitamin D restored cognitive deficits brought on by a high-fat diet (HFD) by lowering concentrations of nuclear factor kappa light chain enhancer of activated B cells (NF-B) and increasing BDNF in the hippocampal region in the brain [65].

Recommendations

Firstly, Screenings for cognitive impairment in high-risk groups and advice on managing diabetes for diabetic patients with cognitive deficiencies. Second, although there are still some questions about the preventive role of vitamin D in the neurodegenerative effects of diabetes, more research in this area is necessary.

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