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REVIEW ARTICLE

Diabetic effect on CNS and the protective role of A. lipoic acid: Review of Literature

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ABSTRACT

Background: Both type 1 and type 2 diabetes have detrimental effects on the central nervous system and increase the risk of cognitive disorders such as Alzheimer's disease. Additionally, there is a proposed condition called "type 3 diabetes" that refers to insulin resistance and impaired insulin signaling in the brain, leading to cognitive deficits similar to those seen in Alzheimer's disease. Diabetes leads to various changes in the CNS, including structural and functional alterations. Chronic high blood sugar levels, oxidative stress, inflammation, and vascular damage associated with diabetes contribute to neuronal damage and impaired synaptic plasticity. Alpha-lipoic acid (ALA) is a naturally occurring compound that acts as a powerful antioxidant.

Conclusions: DM cause damage to CNS through increasing the risk of cerebrovascular diseases, promoting chronic low-grade inflammation, increasing oxidative stress, inducing Alzheimer's diseaseand diabetic encephalopathy. ALA protects against these effects through Improving Insulin Sensitivity, glucose utilization, antioxidant and anti-inflammatory properties.

Keywords: Diabetic encephalopathy; ALA; Thioctic acid ;type 3 diabetes;Alzheimer’s disease

INTRODUCTION

Diabetes mellitus (DM) is a common metabolic disease caused by a deficiency in insulin secretion and/or insulin resistance that cause an excessive rise in blood sugar levels. Persistent hyperglycemia is a hallmark of diabetes mellitus [1].

Effect of Diabetes Mellitus on CNS:

Diabetes increases the risk of cerebrovascular diseases, including ischemic stroke and hemorrhagic stroke. Chronic high blood sugar levels can damage blood vessels in the brain, leading to reduced blood flow or rupture of blood vessels. These vascular changes can affect the cerebral cortex and other brain regions, leading to cognitive impairment and

neurological deficits [2]. Diabetes can contribute to the development of a condition known as diabetic encephalopathy. It is characterized by structural and functional abnormalities in the brain, including neuronal loss, altered synaptic density, and alterations in neurotransmitter systems. The cerebral cortex can be affected, leading to cognitive decline, memory impairment, and executive dysfunction [3].

Diabetes can promote chronic low-grade inflammation in the CNS. Inflammatory processes involving microglial activation and release of pro-inflammatory cytokines can contribute to neuronal damage and dysfunction. Neuroinflammation further exacerbates cognitive impairment and neurodegenerative processes [4].Diabetes is associated with increased oxidative stress, which refers to an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms. Oxidative stress can damage neurons and impair neuronal function. It can contribute to neurodegenerative processes and cognitive decline [5].

The brain has high lipid content and energy demands and that makes it more vulnerable to oxidative damage compared to other parts of the body. Studies indicate that oxidative stress and mitochondrial dysfunction are linked to the accumulation of amyloid-beta (Aβ) plaques, a characteristic feature of AD. Changes in protein processing and the unfolded protein response, such as endoplasmic reticulum stress, can also influence the production of Aβ and are associated with the development of tau protein pathology. Overall, metabolic disorders related to glucose and lipid metabolism, oxidative stress, mitochondrial dysfunction, and protein changes resulting from diabetes contribute to impaired insulin signaling and may increase the prevalence of AD by promoting Aβ pathology. [6]. The term "type 3 diabetes" has been used to describe Alzheimer's disease (AD) due to the presence of insulin abnormalities in the central nervous system (CNS). In AD, there is a deficiency of insulin and resistance of insulin receptors in the CNS, leading to cognitive dysfunction. Insulin plays a crucial role in neurological signaling processes. Additionally, insulin stimulates the expression of the enzyme ChAT, which is responsible for the synthesis of acetylcholine, a neurotransmitter essential for cognition. Furthermore, advanced glycation end products (AGEs), which are found in higher amounts in individuals with diabetes compared to those with normal glucose regulation, have also been observed in high concentrations in the brains of individuals with AD. [7]

The relationship between diabetes and Alzheimer's disease involves multiple mechanisms. Insulin resistance and impaired insulin signaling in the brain may contribute to the accumulation of amyloid-beta protein and tau protein phosphorylation, characteristic of Alzheimer's pathology. Additionally, diabetes-related vascular changes, oxidative stress, and inflammation can further promote neurodegenerative processes in the cerebral cortex, exacerbating the risk of Alzheimer's disease [8-9-10].

Alzheimer's disease is a neurodegenerative disorder characterized by progressive cognitive decline, memory loss, and changes in behavior and personality. It is associated

with the accumulation of abnormal protein aggregates, including beta-amyloid plaques and tau tangles, in the brain. Beta-amyloid plaques form outside neurons, while tau tangles form inside neurons. These abnormal protein deposits disrupt normal cellular function and communication, leading to neuronal damage and cell death. Multiple factors, including genetic, environmental, and lifestyle factors, contribute to its development. [11]. Alzheimer's disease (AD) can be considered a metabolic disease that is influenced by impairments in brain insulin responsiveness, glucose utilization, and energy metabolism. These impairments contribute to increased oxidative stress, inflammation, and worsened insulin resistance. Furthermore, the metabolic disturbances directly contribute to the structural, functional, molecular, and biochemical abnormalities that are characteristic of AD, such as neuronal loss, disrupted synaptic connections, tau hyperphosphorylation, and the accumulation of amyloid-beta plaques. Given that the underlying abnormalities in AD are linked to brain insulin resistance and deficiency, and that the molecular and biochemical consequences overlap with both Type 1 and Type 2 diabetes, the term "Type 3 diabetes" has been proposed to describe the underlying abnormalities associated with neurodegeneration in AD. [12] The effects of diabetes on the CNS can be widespread, affecting various brain regions. However, specific areas commonly implicated include the hippocampus (crucial for memory and learning), the prefrontal cortex (involved in executive functions and decision-making), and the basal ganglia (important for motor control and coordination). [13].The entorhinal cortex (EC) serves as the primary connection between the hippocampus (HIP) and the neocortex, playing a crucial role in long-term cognitive memory formation. EC receives information from multiple senses and communicates it to the HIP using the neurotransmitter glutamate. Studies have shown that AD affects the EC in the early stages of the disease. [14-15].

The hippocampus (HIP) is a region within the temporal lobe that is essential for the formation of new memories. AD often impacts the HIP early and severely, impairing memory function. [16-17]

The middle temporal gyrus (MTG) is located in the temporal lobe and contributes to various cognitive processes, including semantic memory, language processing, and integration of sensory information. Research has demonstrated neuronal loss in the MTG of individuals with AD. [18-19].The posterior cingulate cortex (PC) is a highly connected and metabolically active brain region involved in learning and spatial memory. In AD, amyloid deposition and reduced metabolism have been observed in the PC. Additionally, this region tends to be smaller in size in AD patients compared to healthy individuals. [20-21]. The superior frontal gyrus (SFG) is situated in the superior part of the prefrontal cortex and plays a role in self-awareness, working memory, and cognitive functions such as planning, decision-making, attention, and inhibition. Studies have identified frontal hypo metabolism in relation to AD, indicating impaired functioning of the SFG. [22-23]

The visual cortex (VCX), located in the occipital lobe, receives visual information and

is responsible for visual perception. Damage to the VCX can lead to functional blindness, even if the eyes are correctly transmitting visual input. While some research has explored changes in the VCX associated with normal aging, there is limited information regarding VCX alterations in relation to AD. As the disease progresses, it tends to spread to other areas of the brain, leading to more widespread damage. [24]

Alpha-lipoic acid (ALA), known as Thioctic acid is a naturally occurring compound that functions as a powerful antioxidant in the human body. It is produced in small amounts by de novo synthesis in the body using cysteine and fatty acids and can also be obtained through dietary sources such as organ meats, spinach, broccoli, and potatoes. while the human body produces small amounts of ALA, obtaining it through dietary sources or supplements can significantly increase its availability. [25]

BIOLOGICAL PROPERTIES OF A-LIPOIC ACID ALA:

Antioxidant Activity: ALA is a potent antioxidant that neutralizes free radicals, which are unstable molecules that can cause damage to the cells and tissues. ALA can directly scavenge and neutralize free radicals, reducing oxidative stress and protecting cells from damage [10]. One of the notable properties of ALA is its ability to act as both a fat-soluble and water soluble antioxidant. This unique characteristic allows it to work in different parts of the body, protecting cells and tissues against oxidative stress caused by free radicals. Oxidative stress has been implicated in various chronic diseases and the aging process [9].ALA has participated in the reduction of oxidized and regeneration of reduced forms of other antioxidants, scavenging reactive oxygen species(ROS), because of the dithiolane ring in its molecule [10].

Regeneration of Antioxidants: ALA has the ability to regenerate other antioxidants by converting them back to their active form. For example, ALA can regenerate vitamin C and glutathione, allowing these antioxidants to continue their protective functions in the body. This recycling effect helps to maintain a robust antioxidant defense system [10-27].

Metal Chelation: ALA has metal-chelating properties, which means it can bind to certain metals, such as copper and iron. By chelating excess metals, ALA prevents them from participating in reactions that generate harmful free radicals. This metal-chelating activity contributes to the overall antioxidant capacity of ALA [28-29].

Modulation of Signaling Pathways: ALA has been found to modulate various signaling pathways involved in cellular processes. It can activate certain protein kinases, such as AMP-activated protein kinase (AMPK), which plays a role in energy metabolism and cellular stress response. ALA can also influence gene expression and the activity of transcription factors involved in inflammation and oxidative stress pathways [28-29].

Mitochondrial Function: ALA is known to interact with mitochondria, the cellular organelles responsible for energy production. It plays a crucial role in the conversion of glucose into energy within the mitochondria through its involvement in the Krebs cycle. ALA also maintains mitochondrial function and protects against mitochondrial dysfunction, which is linked to various diseases and the aging process [27]. It

functions as a coenzyme in various metabolic reactions, including the Krebs cycle, which is involved in the production of adenosine triphosphate (ATP), the body's primary energy currency. The mitochondrial energy metabolism is affected byALA, which safeguards the membranes from oxidative damage [31].

Anti-Inflammatory Effects:ALA has been shown to possess anti-inflammatory properties by inhibiting the activity of certain pro-inflammatory molecules, such as nuclear factor-kappa B (NF-κB). By reducing inflammation, ALA may protecttissues from damage and contribute to overall health [32].

ALA has a variety of properties, with particular interest in its antioxidant potential and anti-inflammatory effects in chronic metabolic disorders such as diabetic neuropathies, metabolic syndrome, cardiovascular complications, and neuromuscular complications, where oxidative stress and inflammation are thought to underlie [33]. Additionally, the use of ALA as a therapeutic agent modifies the etiology of inflammation in a number of metabolic disorders. By inhibiting nuclear factor kappa B (NF-κB) kinase, which can limit the release of pro-inflammatory cytokines like interleukin 1 and 6 (IL-1 and IL-6), **Li et al.** showed that this chemical is promise for the pathophysiology of inflammation [32]. More importantly, ALA weakens the formation of prostaglandin E2 by decreasing the activity of cyclooxygenase 2 (COX-2), which affects the profile of prostanoids produced in the later stages of inflammation (PGE2), one of the most powerful lipid metabolites generated from the arachidonic acid (AA), a 20-carbon unsaturated fatty acid [28-30].

The protective role of A. lipoic acid in DM:

Improved Insulin Sensitivity:**Ebada et al.** demonstrated that ALA enhances insulin sensitivity, which is the ability of cells to respond to insulin and pick up glucose from the blood stream by increasing the translocation of glucose transporter proteins (GLUT4) to the cell membrane, allowing for more efficient glucose uptake [34].

Enhanced Glucose Utilization: ALA plays a role in the conversion of glucose into energy within the mitochondria, the cellular powerhouses. By participating in the Krebs cycle and oxidative phosphorylation, ALA facilitates the efficient utilization of glucose, reducing excess glucose levels in the bloodstream [34].**Ebada et al.** demonstrated that ALA has beneficial effects on glycemic control in individuals with diabetes. It can regulate blood glucose levels by increasing glucose uptake and utilization in cells, reducing insulin resistance, and promoting glucose storage in the liver and muscles. By improving glycemic control, ALA may contribute to better overall management of diabetes [34].

Antioxidant Effects:Diabetes is associated with increased oxidative stress, which can contribute to the development of complications. **Tripathi et al.** reported that ALA has antioxidant properties that help to neutralize free radicals and reduce oxidative stress. By protecting cells from oxidative damage, ALA may preserve the function of insulin-producing beta cells in the pancreas and improve overall glucose control [26].

Anti-inflammatory Effects: Chronic low-grade inflammation is often observed in individuals with diabetes**. Salehi et al.** reported that ALA has been shown to possess

anti-inflammatory properties by inhibiting the activity of pro-inflammatory molecules, such as NF-κB. By reducing inflammation, ALA may mitigate the negative impact of inflammation on insulin sensitivity and glucose metabolism [33].

Neuroprotective Effects: Diabetes can lead to peripheral neuropathy, a condition characterized by nerve damage and symptoms such as numbness, tingling, and pain in the extremities. ALA has been investigated for its potential neuroprotective effects and its ability to alleviate symptoms of diabetic neuropathy and protect nerve cells from damage. ALA has antioxidant and anti-inflammatory properties that contribute to its neuroprotective effects [10].

Advanced Glycation End Products (AGEs):Diabetes is associated with the formation of advanced glycation end products, which are harmful compounds that accumulate in tissues and contribute to complications such as diabetic nephropathy (kidney disease). **Niuet al.** reported that ALA has been found to inhibit the formation of AGEs and help break down existing AGEs, potentially reducing the risk of diabetic complications [35].

Nitric Oxide (NO) Production: **Hajizadeh-Sharafabad& Sharifi Zahabi**demonstrated that ALA has been shown to enhance the production of nitric oxide, a molecule that plays a role in regulating blood vessel function and blood flow. Diabetes is associated with impaired nitric oxide production, which can contribute to vascular complications. By increasing nitric oxide production, ALA may improve vascular health and reduce the risk of diabetic complications such as cardiovascular disease [36].

Modulation of Cellular Signaling Pathways: **Kimet al. s**tudies showed ALA modulates various cellular signaling pathways that are dysregulated in diabetes. For example, it can activate the AMP-activated protein kinase (AMPK) pathway, which is involved in energy metabolism and glucose uptake. ALA may also affect other pathways such as protein kinase B (Akt) and nuclear factor erythroid 2-related factor 2 (Nrf2), which are involved in cellular stress response and antioxidant defense [37].

Lipid Metabolism: **Illescaet al. and Ortizet al.** demonstrated that ALA has been shown to influence lipid metabolism, including the breakdown and utilization of fatty acids. It may reduce lipid accumulation in tissues and improve lipid profiles in individuals with diabetes. By promoting healthy lipid metabolism, ALA may contribute to better cardiovascular health and insulin sensitivity [38-39].

Peripheral neuropathy:Diabetic peripheral neuropathy is a common complication of DM, characterized by nerve damage that leads to symptoms such as pain, numbness, and tingling in the extremities. **Elbadawy& Elsayed**demonstrated that ALA has been shown to alleviate symptoms and improve nerve function in diabetic neuropathy. It is believed to protect nerve cells from oxidative stress, reduce inflammation, and enhance blood flow to the nerves [40].

CONCLUSIONS

DM cause damage to CNS through increasing the risk of cerebrovascular diseases, promoting chronic low-grade inflammation, increasing oxidative stress, inducing

Alzheimer's diseaseand diabetic encephalopathy.ALA protects against diabetic effect on CNS through Improving Insulin Sensitivity, enhancing Glucose Utilization, inhibiting the formation of AGEs and help break down existing AGEs, enhancing the production of nitric oxide,Modulation of Cellular Signaling Pathways, enhancing breakdown and utilization of fatty acids and through antioxidant and anti-inflammatory properties.

CONFLICTS OF INTEREST: None.

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