Review article

Hepatopancreatic metabolic disorders and their implications in the development of Alzheimer's disease and vascular dementia

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ABSTRACT

Dementia has been faced with significant public health challenges and economic burdens that urges the need to develop safe and effective interventions. In recent years, an increasing number of studies have focused on the relationship between dementia and liver and pancreatic metabolic disorders that result in diseases such as diabetes, obesity, hypertension and dyslipidemia. Previous reports have shown that there is a plausible correlation between pathologies caused by hepatopancreatic dysfunctions and dementia. Glucose, insulin and IGF-1 metabolized in the liver and pancreas probably have an important influence on the pathophysiology of the most common dementias: Alzheimer's and vascular dementia. This current review highlights recent studies aimed at identifying convergent mechanisms, such as insulin resistance and other diseases, linked to altered hepatic and pancreatic metabolism, which are capable of causing brain changes that ultimately lead to dementia.

1. Introduction

Dementia involves a set of symptoms that develops when the brain is damaged by injury or disease. These often include progressive deterioration of memory, thinking and behavior and, ultimately, the ability to carry out everyday activities (World Health Organization, 2023). Dementia can be caused by many neurological disorders, including Alzheimer's disease (AD), frontotemporal dementia, alcoholic dementia, dementia with Lewy bodies, and vascular dementia (VaD).

The estimated global number of patients with dementia exceeds 50 million. Every year, almost 10 million new cases occur, making dementia the fifth leading cause of death worldwide, while AD is the fourth leading cause of disability-adjusted life years (DALYs) lost in people aged over 75 (Gustavsson et al., 2023; World Health Organization, 2023).

Most cases of late-onset dementia are sporadic and the development of dementia is likely influenced by the complex interplay between genetic risk factors, medical comorbidities, as well as environmental and lifestyle factors (Garcia-Morales et al., 2021; Blaszczyk, 2023). The complexity of dementia goes beyond cognitive symptoms. It affects daily functionality and emotional well-being and burdens healthcare systems and patients' families. As the population age increases, understanding the mechanisms underlying dementia has become crucial to develop effective prevention and treatment strategies (Grossman et al., 2023).

It is believed that the pathophysiology of dementia is associated with the aggregation and accumulation of proteins in a disordered manner, which includes amyloid-beta (Aβ), Tau, alpha-synuclein (α-Syn), and TAR DNA binding protein-43, however, it has also been associated with cerebrovascular disease (CVD), as depicted in Fig. 1 (Bortoletto and Parchem, 2023). On the other hand, changes in the metabolism of

glucose and other substances have been recently identified as important key factors in the pathogenesis of the most common dementias: AD and VaD (Garcia-Morales et al., 2021; Blaszczyk, 2023).

There are two processes involved in the control of glucose metabolism. The first is the insulin-dependent glucose storage in skeletal muscle, liver, and white adipose tissue. The liver is crucial for maintaining normal glucose homeostasis, as it stores glucose after meals and produces glucose during fasting or starvation. In the fasting state, the liver provides glucose to maintain euglycemia and to fuel the brain. Hepatic glucose release is responsible for almost 90% of endogenous glucose production. The hepatic glucose metabolism is regulated by hormones such as insulin, glucagon, catecholamines, corticosteroids and growth hormone (Petersen et al., 2017; Jensen-Cody and Potthoff, 2021).

Glucose, phosphate and oxygen play an essential role in cognitive metabolism. At the cellular level, metabolic crises are usually caused by oxygen, glucose and phosphate deficiencies. The human body transforms the equivalent of body weight into adenosine triphosphate (ATP) daily. The ATP-derived phosphate is then used in multiple phosphorylation cycles, including glucose phosphorylation, which contributes to the regulation of vital neuronal processes required for brain activity and metabolism. In fact, protein phosphorylation regulates interactions between components of neuron-neuron and neuron-glia synergies. In order to maintain the resting membrane potential and to fire an action potential, each pyramidal neuron in cortical networks consumes almost three times more ATP than other neurons. Therefore, an optimum level of phosphate must be provided in order to maintain an adequate neuronal homeostasis (Nazarko, 2019; Blaszczyk, 2023).

Phosphate supply to the brain is controlled by neuronal activity, which makes phosphate the brain's main metabolic stimulator. Serum phosphate homeostasis is maintained through a complex interplay between intestinal phosphate absorption, renal phosphate handling, and cellular phosphate intake. Homeostasis is under hormonal influence of calcitriol, parathyroid hormone and phosphatonins, including fibroblast growth factor 23 (FGF-23). A transient phosphate transport towards active cells is stimulated by insulin or insulin growth factor 1 (IGF-1), glucose, and respiratory alkalosis. Due to limited access to phosphate, increased blood glucose levels can cause hypophosphatemia (Goyal and Jialal, 2023).

Since glucose, insulin and IGF-1 metabolized in the liver and pancreas have important roles in the pathophysiology of dementia, this narrative literature review aims to update the evidence that supports that changes in hepatic and pancreatic metabolism have implications for the development of dementia, especially the vascular type and AD.

2. Methods

This is a narrative review of the literature on studies published between 2000 and 2023 in Science Direct, PubMed, Scientific Electronic Library Online (SciELO), and Latin American Literature in Health Sciences (LILACS) databases, in which the hepatopancreatic metabolic disorders and their implications in the development of vascular and AD
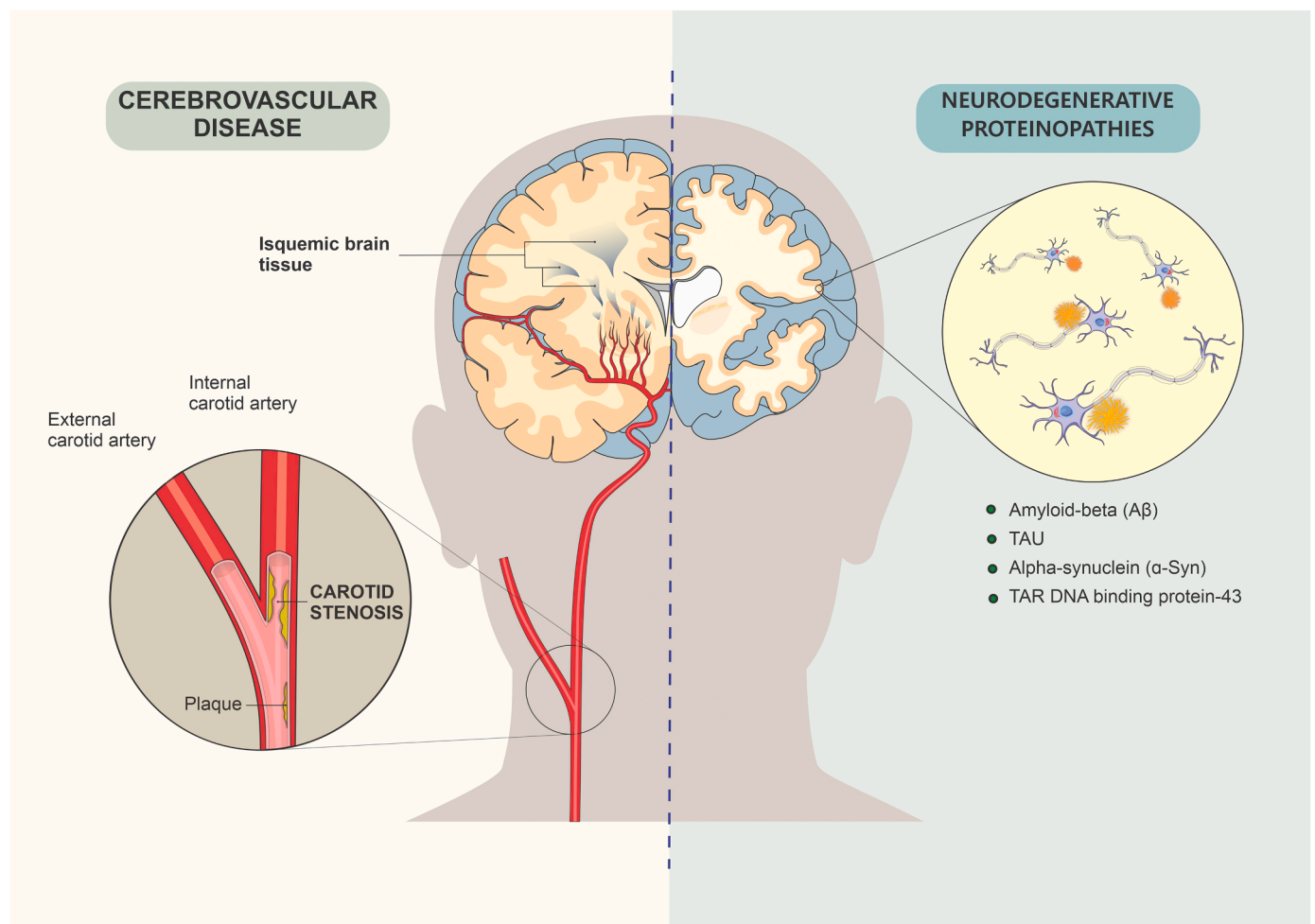

Fig. 1. Representation of neurological disorders due to cerebrovascular dysfunction (on the left) and due to neurodegenerative proteinopathies (on the right). Highlighted are the formation of atheromatous plaques causing carotid stenosis and multiple cerebral infarctions (on the right) and the formation and disarray of amyloid-beta (Aβ), TAU protein, alpha-synuclein (α-Syn), and TAR DNA binding protein-43 (on the left). (Illustration: Francisco Irochima).

dementia were investigated. The search strategy was based on the combination of Medical Subject Headings (MeSH) with "Emtree Terms": "Metabolic disorder and dementia", "Liver disorder and dementia" and "Pancreatic disorder and dementia". In order to further filter the studies in the databases, the Boolean operators "and" or "or" were used with terms to provide a good search strategy.

3. Results

3.1. Hepatic and pancreatic metabolism and its relationship with AD and vascular dementia

Hepatic metabolism and its biochemical processes influence brain functions as much as the overall physical health. The interconnection between liver metabolism and mental health reveals surprising connections between the liver and the brain. Recent studies, such as those by Wang et al. (2023), shed light on this relationship, highlighting the complexity and importance of such organic interactions. Therefore, the intersection between hepatic metabolism and dementia is an essential field of study. In fact, when analyzing the results of a series of studies, complex connections are observed in the mechanisms involving the onset of dementia, specially AD, and hepatic metabolism (Gao et al., 2023, Wang et al., 2023).

In the same way, the relationship between pancreatic metabolism and AD/vascular dementia is a fascinating and expanding area of research. Several factors contribute to the increased risk of patients with pancreatic metabolism dysfunction to develop dementia. One important factor involves the toxic accumulation of amylin, or islet amyloid polypeptide (IAPP). Biologically active monomeric IAPP is co-secreted with insulin by pancreatic β-cells and it works as a hormone that assists in regulating metabolism and signaling satiety (Bortoletto and Parchem, 2023). As insulin secretion increases with hyperglycemia in diabetic and prediabetic patients, there is also a simultaneous increase in IAPP secretion. IAPP is prone to aggregation and the increase in its levels can lead to the formation of toxic oligomers in the pancreas, which is similar to what occurs with other amyloidogenic peptides such as Aβ. Although amyloid fibrils and plaques can lead to cell death, recent data suggest that the most cytotoxic form of amyloid is the prefibrillar or protofibrillar. Because monomeric IAPP is soluble in serum and IAPP protofibrils can cross the blood-brain barrier, aggregation of IAPP in the brain seems to contribute to neurodegeneration (Camargo et al., 2018).

One of the central aspects linked to cognitive decline is the metabolism of tryptophan, a precursor to serotonin. Liu et al.(2019) and Chen et al.(2021) observed the direct influence of the liver on tryptophan metabolism. The liver is responsible for metabolizing tryptophan, affecting its availability in the brain. The kynurenine pathway has recently been identified as a promising target to increase healthy longevity. It originates from tryptophan and represents another link between liver and cognitive decline (Savitz, 2020; Castro-Portuguez and Sutphin, 2020). The metabolic processing of tryptophan through the kynurenine pathway produces a range of biologically active intermediate metabolites. One branch of the pathway ultimately leads to the synthesis of nicotinamide adenine dinucleotide (NAD+), which is an essential cofactor that plays a critical role in many enzymatic redox reactions and energy production by mitochondria. NAD levels decline with age in several tissues, including the brain. In fact, this decline has been considered as a risk factor in the pathophysiology of several categories of age-associated diseases, such as AD and vascular dementia (Castro-Portuguez and Sutphin, 2020; Fernandes et al., 2023).

Therefore, increasing the NAD+ levels through its precursors has the potential to prevent or alleviate a wide range of diseases, such as metabolic disorders and dementia. Based on their ability to elevate NAD+ levels, nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) are NAD+ precursors that have been shown to attenuate physiological decline, diabetes, protect against liver disease, decrease the risk of AD, protect neuronal cells from oxidative stress and

preserve cognition (Nadeeshani et al., 2021; Alegre and Pastore, 2023). When administered to mouse models of AD, NR increased NAD+ levels which resulted in beneficial effects on both oxidative stress and DNA repair (Gong et al., 2013). Furthermore, NR may improve other aspects of AD neuropathology, including pTau, Aβ, neurogenesis, neuroinflammation, hippocampal synaptic plasticity and cognition (Hou et al., 2018; Mehmel, Jovanovic and Spitz, 2020).

In addition to hepatic metabolism, the intestinal microbiota is a relevant element in mental health (Evrensel et al., 2020; Collier et al., 2021). Although microorganisms that inhabit the intestine play a role in the metabolism of NAD+ and its metabolites, it has been reported that NMN and NR also affect the composition of the intestinal microbiota, therefore reversing dysbiosis and promoting beneficial effects at both intestinal and extraintestinal levels (Huang et al., 2021; Alegre and Pastore, 2023). It is well known that intestinal dysbiosis negatively affects hepatic metabolism as well as the intestine-brain axis, therefore it can affect the production of neurotransmitters and inflammatory modulation, which may alter mood and cognition (Gheorghe et al., 2019; Hyland et al., 2022). Fig. 2 depicts the relationship between intestinal dysbiosis and liver dysfunction, leading to changes in the gut-brain axis with the potential to trigger mental disorders such as dementia (Grifka-Walk et al., 2021; Więdłocha et al., 2021).

Many of the important functions of insulin in the brain are disrupted under conditions of insulin resistance, which can occur in people with liver and pancreas disorders. Prolonged peripheral hyperinsulinemia associated with insulin resistance reduces insulin transport across the blood-brain barrier (BBB), subsequently decreasing insulin levels and activity in the brain. This effect may be associated with the reduced cerebrospinal fluid insulin levels and brain markers of insulin signaling that are commonly observed in patients with AD (Craft, 2009). Insulin resistance and hyperinsulinemia are observed in several pathophysiological processes related to AD. Reduced insulin signaling in the brain is associated with increased tau protein phosphorylation and Aβ levels in a streptozotocin mouse model of diabetes (Craft, 2009). Insulin also induced the release of intracellular Aβ in neuronal cultures and accelerated the Aβ transport to the plasma membrane. In humans, increasing plasma insulin levels via intravenous infusion increases cerebrospinal fluid levels of the Aβ42 peptide (Craft, 2009; Minamisawa et al., 2022).

Diabetes increases the risk of AD and vascular dementia regardless of the age at which diabetes occurs (Craft, 2009). The mechanisms that justify this increased risk are associated with the effects of insulin resistance, which includes the increased levels of advanced glycation end products related to hyperglycemia as well as oxidative stress, inflammation and macrovascular/microvascular injury (Craft, 2009; Hughes and Craft, 2016).

3.2. Hepatic metabolism and Alzheimer's disease

Recently, the role of hepatic metabolism in dementia has emerged as an innovative and promising area of research. Studies demonstrate that liver dysfunction triggers direct events in the central nervous system that play an active role in the pathogenesis of dementia (Barone, 2019; Evrensel et al., 2020; Więdłocha et al., 2021).

Several studies address the role of changes in the intestinal microbiota, hepatitis, tryptophan pathway, and kynurenine, in the genesis of AD. Such studies corroborate the participation of inflammatory cytokines in the pathophysiology of neurological diseases and emphasize the role of hepatic metabolism in the search for new therapeutic approaches, including nutritional treatments, lifestyle changes, and even electroconvulsive therapy in the most severe cases (Garcez et al., 2019; Gostner et al., 2020; Mithaiwala et al., 2021; Aarsland et al., 2022; Hyland et al., 2022; Sharma et al., 2022).

It is crucial to mention the growing research into the role of hepatic metabolism in neurodegenerative disorders, such as AD. Garcez et al. (2019) and Tsuji et al.(2023) explore the complex connections between tryptophan metabolism and the pathogenesis of these diseases, offering
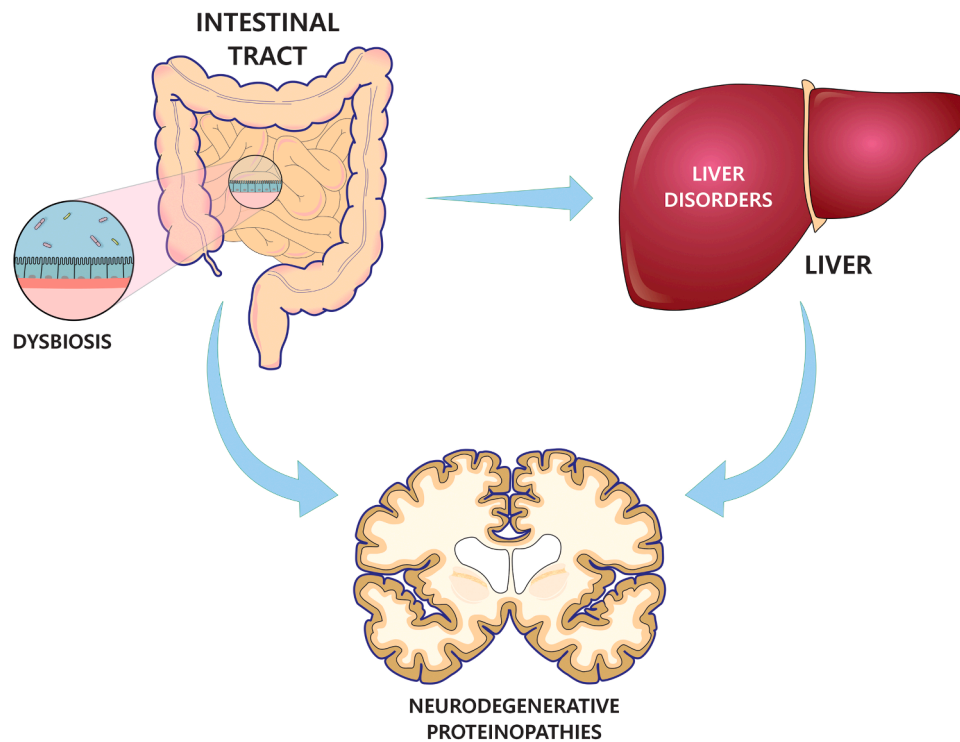
Fig. 2. Diagram demonstrating that intestinal dysbiosis can lead to liver dysfunction and both can result in brain dysfunction such as proteinopathies, which is proven to be linked to the pathogenesis of dementia. (Illustration: Francisco Irochima).

valuable insights for future therapeutic interventions. These studies suggest that the liver plays a key role in mental health by preventing the progression of neuropsychiatric disorders, including dementia (Garcez et al., 2019a; Tsuji et al., 2023).

The conversion of tryptophan (TRP) to kynurenine (KYN) is responsible for more than 95% of all TRP catabolism. The first and limiting step in this pathway is the conversion of TRP to KYN by the enzymes IDO and TDO (Badawy, 2017). TDO is mainly produced in the liver and is responsible for the majority of KYN production, while IDO exists in two subtypes, IDO-1 and IDO-2. IDO-1 is produced in different tissues as an anti-inflammatory signaling pathway of negative immune regulation, while IDO-2 is less common. This makes the kynurenic pathway (KP) of particular interest for the study of neurodegenerative diseases such as AD (Savonije and Weaver, 2023). Tryptophan and its associated metabolites are capable of inhibiting several enzymes that participate in Aβ biosynthesis, but one metabolite, 3-hydroxyanthranilate, is capable of directly inhibiting Aβ oligomerization. Although certain tryptophan metabolites are neuroprotective, other metabolites, such as quinolinic acid, are neurotoxic and may contribute to the progression of AD (Huang et al., 2023).

In this context, the gut-brain axis emerges as an area of scientific interest. Changes in the microbiome's composition, influenced by hepatic metabolism, modulate inflammation in the brain and contribute to the pathogenesis of dementia (Wiedlocha et al., 2021). Mahmoudian Dehkordi et al.(2019) analyzed the complexity of the intestinal microbiome and its influence on AD. An association was observed between changes in bile acids and cognitive decline, which corroborates the intestine-brain interaction (Mahmoudian Dehkordi et al., 2019). Intestinal dysbiosis is able to alter intestinal permeability and potentially increase BBB permeability through altered secretion of short-chain fatty acids (SCFA), which may lead to secretion of harmful compounds that result in systemic inflammation and cognitive impairment (Westfall et al., 2017). In fact, systemic inflammation has been linked to reduced cognitive function, especially short-term memory and verbal learning (Escobar et al., 2022).

Several foods can alter the composition and quantity of numerous species of intestinal bacteria, which contributes to maintaining intestinal homeostasis. Long recognized as a healthy eating plan, the Mediterranean diet (MD) includes considerable amounts of vegetables, legumes, fruits and grains (Long-Smith et al., 2020). One study confirmed that greater adherence to MD can protect against brain aging and AD for up to 3.5 years, besides reducing the progression of dementia (Berti et al., 2018). Human-based studies indicate that a diet rich in fruits, vegetables and legumes, consistent with MD, can modify intestinal flora, increase fecal SCFA levels and reduce urine Trimethylamine N-oxide (TMAO) levels, which prevent systemic inflammation and reduce the release of harmful compounds that increase the risk of AD development (Filippis et al., 2016).

Furthermore, recent studies have revealed that insulin resistance, associated with some metabolic conditions, plays a crucial role in the development of dementia, thus directly linking liver function and brain health (Pelle et al., 2023). By exploring the molecular reasons for brain insulin resistance, Cetinkalp et al. (2014) identified the underlying mechanisms involved and the potential therapeutic strategies. This study made the direct relationship between insulin regulation and cognitive decline even more evident (Cetinkalp et al., 2014).

Talbot et al. (2012) showed that insulin receptor resistance in the brain occurred in most of the individuals with AD, even though diabetes mellitus was absent in the majority of them, which indicates that CNS insulin resistance was present even in the absence of peripheral insulin resistance (Talbot et al., 2012). Deficient insulin activity in the CNS can be due to insufficient amounts of insulin as a result of its reduced ability to enter the CNS, which could originate from an incapacity of the BBB to efficiently transport insulin to the brain. Evidence for this phenomenon includes a lower CSF/serum insulin ratio in individuals with AD when compared with individuals without AD (Rhea et al., 2022).

Kochkina et al. linked age and diabetes to insulin degradation in specific tissues, highlighting the mechanisms underlying metabolic changes associated with age-related dementia. This study provided a critical understanding of how changes in insulin metabolism are

intrinsically linked to Alzheimer's progression (Kochkina et al., 2015).

In summary, insulin resistance and its metabolic disorders are directly associated with the pathogenesis of AD. Insulin is crucial in normal brain function, maintaining synaptic plasticity, energy metabolism, tau homeostasis, and protection against oxidative stress and neuroinflammation (Parfenov et al., 2019). Elevated peripheral insulin levels are associated with worsening cognitive function. However, there are many conditions associated with insulin resistance that are also linked to AD, including hyperlipidemia, hyperthyroidism, and hyperglycemia. Many features of peripheral insulin resistance can have indirect effects on the CNS and they are usually linked to a BBB disruption. For instance, as peripheral insulin resistance is often associated with hyperglycemia, hyperinsulinemia, and increased lipolysis that leads to an increase in serum free fatty acids (FFAs), such alterations affect the transport of critical metabolic hormones, potentially increasing the risk of AD (Banks, 2019; Rhea et al., 2022).

Insulin resistance and hyperinsulinemia promote tau hyperphosphorylation, contributing to the pathogenesis of AD. Insulin resistance is also associated with oxidative stress, neuroinflammation, endothelial dysfunction, dyslipidemia, and increased blood-brain barrier permeability (Vishnu et al., 2017; Anjum et al., 2018).

3.3. Hepatic metabolism and vascular dementia

VaD affects cognition as a result of a reduced cerebral blood flow. It has been associated with slow thinking, forgetfulness, depression, anxiety, and disorientation, all of which interferes with reasoning, judgment, planning, and execution of normal tasks (Garcia and Brown, 1992; Luoma, 2011).

VaD affects 17–20% of all patients, being the second form of dementia after AD. VaD includes small vessel strokes (SVD) and cytokine-mediated vasculitis. Hypertension, diabetes, and metabolic syndrome are pathologies associated with VaD (Pedersen and Febbraio, 2005; Silva et al., 2022). As the population ages, the prevalence of vascular dementia increases. Regarding etiology, the accumulation of Aβ promotes the hyperphosphorylation of Tau, which is associated with cellular damage, oxidative stress, mitochondrial dysfunction, inflammation, and neuronal apoptosis (Alemi et al., 2016; Giannisis et al., 2022).

Among the risk factors, diabetes doubles the risk of VaD, especially in patients >65 years old. Diabetes and peripheral arterial disease are independent risk factors for vascular dementia, mediated by microvascular infarcts and neuroinflammation (Jensen et al., 2020; Shang et al., 2022).

Metabolic syndrome (MS) is another risk factor, which includes abdominal obesity, hypertension, and dyslipidemia with low HDL associated with insulin resistance. It is inferred that high triglyceride levels and diabetes increase the risk of VaD over time, especially in patients aged > 65. Vascular dementia induced by MS results from reduced cerebral blood flow (CBF), which is responsible for short-term memory loss in patients with an average age of 60.4 years, obese, and with hypertriglyceridemia. Therefore, there is a progression from mild cognitive impairment to dementia that is intrinsically linked to neuronal damage (Bassendine et al., 2020; Panyard et al., 2023).

VaD derives from severe cerebral vascular impairment in thalamic, frontal, and temporal lobe regions. It can also derive from thromboembolic phenomena, which, even if minor, cause severe vascular injuries. The main etiological factor of VaD is small vessel disease (SVD). SVD induces isolated lacunar infarcts and ischemic lesions in cognitive brain areas. Multiple-infarct dementia derives from cerebral microinfarctions, which promote cognitive deficits when they affect reasoning-related areas (Gehrke and Schattenberg, 2020; Weng et al., 2022).

Current evidence infers that hepatic metabolism disorders play a key role in the etiology of dementia and cognitive impairment as a result from changes in glycemic metabolism, peripheral insulin resistance, and mitochondrial function. Such phenomena interfere with the clearance of Aβ bodies and inflammatory cytokines, which are essential in the metabolic control from the interaction between the glucose/insulin and macronutrients (glucose, lipids, and proteins) (Chen and Zhong, 2014; Smith et al., 2020).

The liver transforms macronutrients into usable or storable compounds, maintaining the balance of energy metabolism and interacting with the pancreas and adipose tissue. The liver, pancreas, muscles, and adipose tissue act upon hyperglycemia, preventing this phenomenon from compromising cerebrovascular function in the long term (Li et al., 2017; Kheirbakhsh et al., 2018).

Alterations in tryptophan metabolism in the aged population contribute to the occurrence of vascular complications, progressive neurodegeneration and cognitive impairment. In the liver, tryptophan catabolism by indoleamine 2,3-dioxygenases (IDO1/2) through the kynurenine pathway (KP) leads to the generation of multiple bioactive metabolites called kynurenines. Activation of IDO-1 and KP could possibly result in vascular dementia directly through vasoactive metabolites and/or indirectly by stimulating iNOS through multiple pathways. Several KP metabolites can have a direct effect on blood vessels, causing arterial stiffness mediated by vascular inflammation and atherosclerosis through binding to aryl hydrocarbon receptors (Mahalakshmi et al., 2022).

Glucose is crucial for the brain as it supports optimal neuronal, microglia, and astrocyte functions. The scarcity of glucose in the brain results in ketogenesis. In addition, the insulin stimulation in the brain helps vagal nerve activity in the liver, accelerating glycogen synthesis, therefore, controlling glucose production in the liver and removing glucose from circulation. The afferent innervation from the liver to the brain is fundamental in releasing epinephrine and cortisol in response to insulin-induced hypoglycemia (Mahmoudian Dehkordi et al., 2019; Nunes et al., 2022).

The discovery of the liver-brain complex demonstrates the role of the liver in the genesis of vascular dementia. This phenomenon is observed in the presence of liver pathologies, whether in non-alcoholic fatty liver disease (NAFLD), viruses, post-transplants and alcoholic cirrhosis, as such pathologies significantly affect cognitive function and predispose to vascular dementia (Bosoi et al., 2020; Sweetat et al., 2023).

In addition to glucose metabolism resulting from the interaction of the liver, pancreas, muscles, and adipose tissue, it is worth mentioning the biochemical processes linked to fatty acids, ketones, pyruvate, and oxidative reactions that culminate in the production of acetyl CoA. This latter interferes in the supply of neuronal glucose, metabolism of essential amino acids, triglycerides and deposits of Aβ compounds in the brain, considering that 50% of the Aβ produced in the brain is eliminated peripherally, with the liver being the leading site of clearance (Shalimova et al., 2019; Ortiz et al., 2022). In this sense, it is no coincidence that reduced levels of alanine transaminase and an increased proportion of aspartate aminotransferase are considered as risk factors for the onset of VaD (Ortiz et al., 2022).

In the liver-brain context, mitochondrial function is modulated by mitophagy, mitochondrial fission and fusion, oxidative stress, and proteins through nutrient detection pathways. Mitochondrial function and insulin are closely related as insulin resistance contributes to mitochondrial dysfunction and, through a feedback mechanism, systemic insulin resistance promotes mitochondrial neuronal dysfunction, which is another factor linked to dementia (Wang et al., 2022).

This process is explained by the deposition of Aβ/Tau. Additionally, mitochondrial dysfunction leads to a cascade of neurotransmitter release, oxidative stress, lipid peroxidation of plasma membranes, oxidation of structural enzymes, and irreversible changes in calcium homeostasis, all of which are observed in VaD. The entire process is mediated by inflammatory factors, which is no different regarding liver metabolic dysfunction and its association with AD or VaD (Sun, 2018).

Brain inflammation in people with dementia is characterized by an increase in circulating cytokines IL-6, IL-1β IL-18, TGF-β, TNF-α, α-1

antichymotrypsin, and C-reactive protein. Therefore, there is a direct correlation between peripheral inflammation and cognitive dysfunction. The inflammatory process activates brain macrophages (microglia) and other immune cells, exacerbating Aβ/Tau-related pathologies (Angelopoulos et al., 2008).

In summary, insulin resistance is an essential link between metabolic disorders and the pathogenesis of vascular dementia. Insulin is crucial in normal brain function, maintaining synaptic plasticity, energy metabolism, Tau homeostasis, and protection against oxidative stress and neuroinflammation (Parfenov et al., 2019).

Insulin resistance and hyperinsulinemia result in dysfunctional vessels of the central nervous system, contributing to the pathogenesis of VaD. Insulin resistance is associated with vascular infarction, oxidative stress, neuroinflammation, endothelial dysfunction, dyslipidemia, and increased blood-brain barrier permeability (Vishnu et al., 2017; Anjum et al., 2018).

Finally, the liver acts upon inflammation through the release of cytokines and inflammatory secretions, especially over time during the aging process, which is amplified by the presence of diabetes, hepatic steatosis, and other metabolic and mitochondrial dysfunctions that ultimately culminate in oxidative stress, in the release of oxygen free radicals, as well as in the activation of microglia and recruitment of brain monocytes (Custodero et al., 2022).

3.4. Pancreatic metabolism and Alzheimer's type dementia

As the main source of energy for the brain, glucose is metabolized into ATP, an unstable high-energy compound. Thus, the glucose metabolism in the brain involves several steps, in which the initial phase comprises the receiving of signals by the brain to trigger glucose uptake via insulin signaling. Next, the physiological process of glucose uptake occurs, which is dependent on the dissemination of glucose transporters (GLUTs) throughout the brain, allowing glucose to cross the blood-brain barrier and reach neurons through astrocytes (Molofsky et al., 2012; Arnold et al., 2018).

The presence of insulin in the brain activates insulin receptors located on the membrane of neurons and astrocytes, which are highly concentrated in the olfactory bulb, cerebral cortex, hippocampus, hypothalamus, amygdala and septal area. The interaction of insulin with its respective receptors in the hippocampus and medial temporal cortex directly influences memory. One of the memory-related mechanisms includes the modulation of synaptic structure and function, which plays an essential role in neuronal growth and differentiation (Zhao and Townsend, 2008; Sedzikowska and Szablewski, 2021).

Reduced glucose signals result in impaired glucose uptake in the brain with AD due to reduced expression of GLUT1 and GLUT3 at the blood-brain barrier (Huang et al., 2020). Thus, decreased expression of insulin-sensitive GLUTs is strongly associated with a decline in glucose uptake, as insulin and insulin receptors are essential factors in regulating glucose utilization and energy homeostasis between CNS and peripheral circulation (Taguchi et al., 2007).

The human brain uses about 20–25% of the body's total glucose consumption to carry out synaptic activity. Primarily, changes in glucose utilization hinder natural cellular functions, including synaptic functions in the brain. Typically, insulin receptors in the brain cells control the process of glucose consumption and metabolism. Since neurons require excess energy to maintain their normal activities, a metabolic decline in the brain contributes to the development of cognitive complications. Thus, changes in the cerebral metabolic rate of glucose and glucose consumption are reflected in synaptic excitability and neuronal activity (Boveris and Navarro, 2008; Mosconi et al., 2008).

The development of insulin resistance significantly increases the risk of AD, in addition, type 2 diabetes (T2D) increases the risk of AD by 50% (Li et al., 2015; Ferreira et al., 2018; Hayden, 2019; Yu et al., 2020). In fact, a reduction in glucose consumption in the hippocampus and posterior cingulate has been observed in the early stages of AD (Protas et al.,

2013; Ferrari et al., 2019; Chen et al., 2021).

In the advanced stages of dementia, glucose consumption is reduced in several brain lobes. Furthermore, the decline in glucose metabolism affects synaptic density and function, suggesting that functional impairment has a connection to brain glucose consumption (Sanabria-Diaz et al., 2013; Shivamurthy et al., 2015).

Oxygen and glucose metabolic rates are drastically altered in many neurodegenerative diseases, including AD due to marked changes in the glycolytic pathway and tricarboxylic acid cycle (Hoyer, 1982; Arias et al., 2002; Van Gijsel-Bonnello et al., 2017).

In T2D, the body becomes resistant to insulin, forcing the pancreas to produce increasing amounts of insulin to induce the uptake of glucose by cells. Thus, systemic insulin resistance attenuates the procognitive effects of insulin in the brain and, as a result, insulin resistance is associated with decreased verbal fluency, low gray matter volume in the temporal lobes, and declarative memory deficiencies (Kim and Feldman, 2015; Walker and Harrison, 2015; Neth and Craft, 2017).

T2D has been associated with the induction and amplification of neuroinflammation in the AD's brain (Van Dyken and Lacoste, 2018; Rom et al., 2019; Hsieh et al., 2019). One of the mechanisms is due to the fact that T2D slows down the glucose catabolic process and reduces the levels of the antioxidant pyruvate (Rodic and Vincent, 2018; Bishayee et al., 2022). Furthermore, the accumulation of Aβ plaques induces oxidative stress and protein misfolding-related stress (ER stress) through impairment of mitochondrial redox potential. Alternatively, ROS accumulation increases abnormal phosphorylation of Tau protein via glycogen synthase kinase 3 (GSK3) and increases apoptosis signal-regulating kinase Axis 1 (ASK1)–p38 MAPK in aging brain with AD (Kadowaki et al., 2005; Song et al., 2014; Hasegawa et al., 2018; Llanos-Gonzalez et al., 2019).

Accumulation of unused glucose due to unresponsive insulin receptors in T2D contributes to hyperglycemia and might result in several cytotoxic complications. Hyperglycemic protein misfolding is a common problem related to T2D, where misfolded protein deposits, composed of Aβ and Tau protein, are able to trigger proteinopathies in AD (Mukherjee et al., 2015; Hetz and Saxena, 2017).

A crucial feature of AD includes impaired insulin signaling in the brain, classifying this dementia as type 3 diabetes due to the consequences of insulin resistance on memory decline and impaired cognitive function (Craft et al., 1998; Kandimalla et al., 2017; Rorbach-Dolata and Piwowar, 2019). Therefore, disorders directly related to changes in pancreatic metabolism, such as T2D, hyperlipidemia and obesity, lead to an increased risk of developing AD (Neth and Craft, 2017; Zhang and Liu, 2018).

Insulin transport to the brain can be negatively regulated by peripheral insulin resistance, which can affect glucose metabolism in the CNS, contributing to oxidative stress and inhibiting the neurotrophic effects of insulin. At the same time, as absolute levels of insulin are increasingly higher (although the effect is diminished), hyperinsulinemia leads to the formation of peripheral and central Aβ plaques, similar to those observed in the neuropathology of AD and other neurodegenerative diseases. These Aβ plaques can activate inflammation in the CNS, leading to more neuronal death (Blazquez et al., 2014; de Nazareth, 2017).

Amyloid plaques formed by Aβ polypeptides also play an important role in AD-induced insulin signaling disorder by binding to the insulin receptor in the brain (Bosco et al., 2011; Ahmed et al., 2015). Insulin and insulin growth factor 1 (IGF-1) signaling help maintain and control metabolism and cognition in the CNS, with insulin resistance being one of the main risk factors for AD (de la Monte and Wands, 2005; Diehl et al., 2017).

It is well known that homeostatic glucose metabolism in the brain is highly associated with cognitive resilience. Therefore, a reduction in glucose uptake in important areas of the brain hinders the necessary glucose support for neuronal activity, leading to reduced cognitive function. In this sense, reduced glucose metabolism in the brain is

associated with insulin resistance, which has been linked to exacerbation of Aβ deposition (Ahmed et al., 2015; Bharadwaj et al., 2017; de Nazareth, Hammond et al., 2020).

Glucose is the main source of energy for the brain and peripheral changes in blood glucose concentration can affect cognitive performance in healthy individuals (García et al., 2021). Keeping high levels of glucose in the blood for a long time, for example, through the consumption of large quantities of foods containing high amounts of glucose or other types of sugar (fructose, sucrose), may be implicated in neuropathological mechanisms typically found in individuals with insanity. Some of these processes may include, but are not limited to, microvascular damage, impaired glucose metabolism, and increased Aβ deposition, each of which may independently exacerbate cognitive decline or elevate the risk of dementia (García et al., 2021; Kirvalidze et al., 2022).

In elderly subjects without cognitive impairment, glucose uptake in the bilateral anterior cingulate cortex and anterior temporal pole has shown to be highly correlated with global cognition, despite the Aβ deposits that were observed in these subjects along with their positive APOE ε4 status (Arenaza-Urquijo et al., 2019). Dysregulation of metabolism is also related to inflammatory responses, particularly in microglia. Thus, increased levels of Aβ protein can directly activate microglia to produce inflammatory factors, changing the metabolism of OXPHOS to aerobic glycolysis (Baik et al., 2019).

Another factor that is worth mentioning is the dysregulation of amylin (or islet amyloid polypeptide; IAPP), which is a hormone produced by the pancreas that plays an important role in regulating energy metabolism. Fig. 3 shows how increased insulin resistance and hyperglycemia generated in the liver causes hyperphosphorylation of the TAU protein, as well as an increase in free radicals and neuroinflammation, all of which can lead to AD. Therefore, the occurrence of amylin imbalance (or islet amyloid polypeptide; IAPP), as observed in obesity and diabetes, may contribute to the accumulation of Aβ plaques in the CNS.

Since this hormone competes with pathological Aβ proteins for receptor binding sites and even helps eliminate amyloid from the CNS, it has a direct implication in inflammatory regulation and neuronal death (Lutz and Meyer, 2015; Bharadwaj et al., 2017; Reiner et al., 2017).

Previous studies have reported that decreased glucose uptake in the brain is a better marker for classifying AD than the deposition of Aβ or phosphorylated Tau. Aβ and Tau are better predictors of early dementia, which is often defined as mild cognitive impairment, while low glucose uptake is a better predictor of later dementia or clinical AD. Thus, Aβ may be an appropriate target for early AD treatment, whereas glucose metabolism should be investigated as a target for late AD treatment (Oboudiyat et al., 2013; Blennow and Zetterberg, 2018; Jack et al., 2018; Hammond et al., 2020).

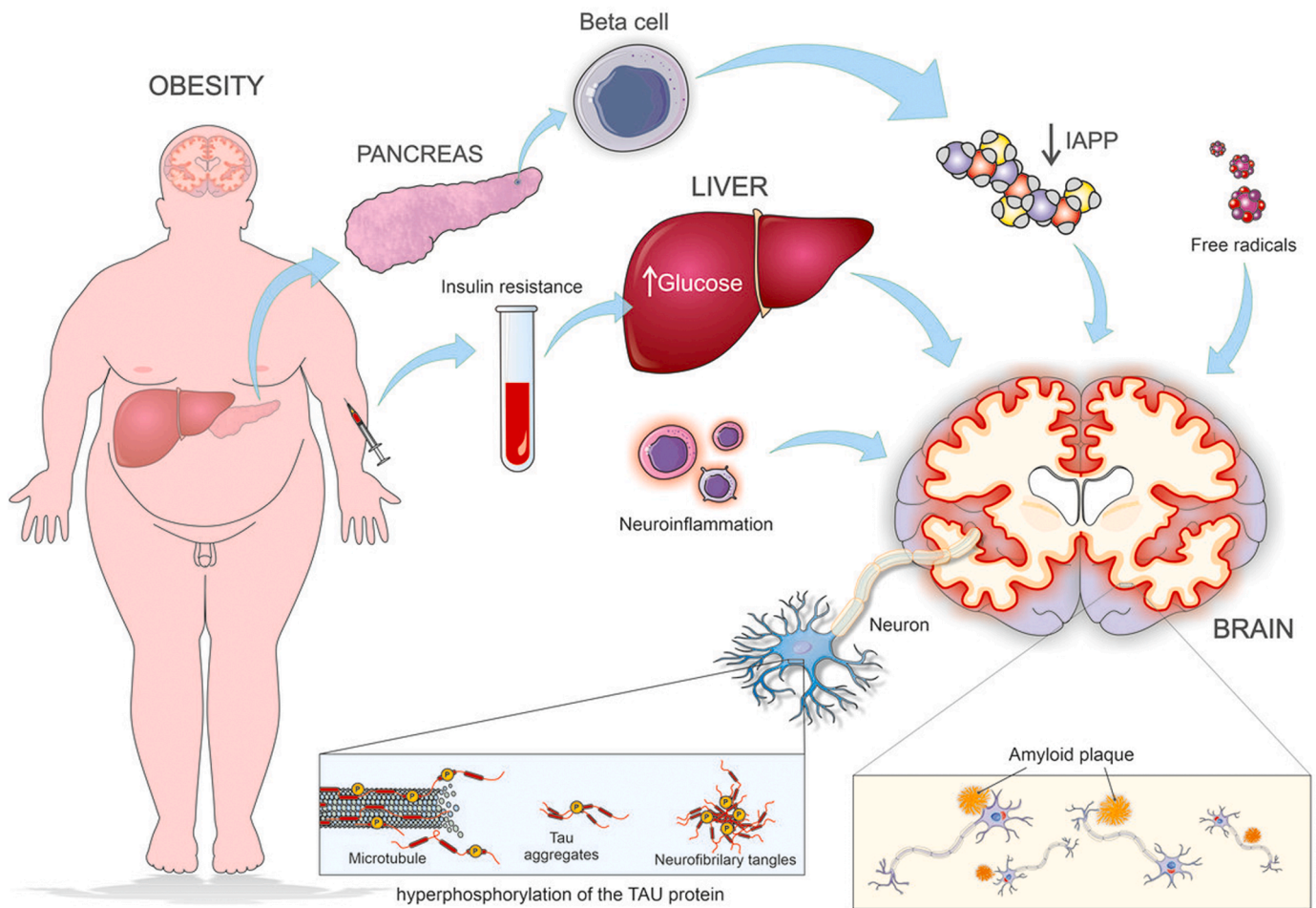Therapies involving the regulation of glucose metabolism and insulin

Fig. 3. Insulin resistance leads to hyperglycemia due to increased glucose production in the liver, which also results in higher levels of free radicals, neuroinflammation with an increase in interleukins and hyperphosphorylation of the TAU protein. These processes ultimately result in varying degrees of neurodegeneration. (P- phosphorus). Furthermore, the decrease in amylin (or islet amyloid polypeptide; IAPP) produced by pancreatic beta cells in obese and type 2 diabetic patients contributes to Aβ plaque deposition in the central nervous system (CNS). This occurs because insulin competes with Aβ proteins for binding sites on specific receptors, helping to eliminate amyloid material from the CNS, in addition to having a direct implication in inflammatory regulation and neuronal death (Illustration: Francisco Irochima).

resistance may be an important step in regulating mitochondrial dysfunction as well as changes in cholesterol metabolism as a result of aging and other AD risk factors (Liu et al., 2013).

3.5. Pancreatic metabolism and vascular dementia

Vascular cognitive impairment is a syndrome with evidence of clinical or subclinical stroke in which vascular brain injury and cognitive impairment affect at least one cognitive domain, such as executive/attention, memory, language and visuospatial function (Hachinski et al., 2006; Gorelick et al., 2011; Sachdev et al., 2014).

Insulin resistance has many negative effects on vascular function that are directly related to impaired insulin activity as this hormone plays an important role on the vasoreactivity and hemodynamic functions, such as capillary recruitment, vasodilation and regional blood flow (Cersosimo and DeFronzo, 2006; Iadecola and Davisson, 2008; Viswanathan and Greenberg, 2011).

Since insulin increases nitric oxide-mediated vasodilation and regulates vasoconstriction via endothelin-1, insulin resistance decreases nitric oxide and increases endothelin-1 activity, favoring vasoconstriction and reducing capillary recruitment. On the other hand, endothelial dysfunction reduces insulin transport, thus reducing capillary recruitment and microvascular blood flow, which exacerbates glucose and lipid abnormalities, establishing a negative feedback loop between progressive endothelial dysfunction and increased insulin resistance. In the brain, vasoconstriction and reduced capillary recruitment can interfere with the functions of the neurovascular unit, as well as with the coordinated interaction between astrocytes, neurons and endothelium (Cersosimo and DeFronzo, 2006; Iadecola and Davisson, 2008).

An adequate blood supply to the brain parenchyma is necessary for essential functions such as neuronal activity, blood-brain barrier function, and immune cell surveillance. Therefore, interruption of blood flow to this tissue is associated with a series of neurovascular dysfunctions, which includes endothelial dysfunction, glial activation, demyelination and breakdown of the blood-brain barrier, as observed in the vascular cognitive impairment of patients with dementia (Gorelick et al., 2011; Wallin et al., 2009; Bouhrara et al., 2018; Low et al., 2021).

Fifty percent of hypertensive patients are insulin resistant and manifest endothelial dysfunction as a result of the direct activity of insulin resistance on vasoreactivity and microvascular blood flow, as well as of its indirect activity on dyslipidemia and inflammation. Hypertension impairs functional hyperemia, the process by which brain activity and blood flow are coordinated. This impairment is induced by dysregulation of vasoactive mediators such as NO and endothelin-1, as well as oxidative stress, structural changes in blood vessels and inadequate cerebral autoregulation (Cersosimo and DeFronzo, 2006; Iadecola and Davisson, 2008).

Previous reports suggest that chronic cerebral hypoperfusion, as a result of vascular disease, may directly influence on the pathophysiology of vascular cognitive impairment (Román, 2004; Hilal et al., 2017; O'Brien et al., 2003; Van Der Flier et al., 2018). Thus, chronic cerebral hypoperfusion is involved in the development of vascular cognitive impairment, as it is closely associated with a series of important physiological vascular changes and cognitive decline (Duncombe et al., 2017; Wolters et al., 2017). It is well established that chronic cerebral hypoperfusion damages the structure of the brain's white matter, which results in declining executive function and memory, therefore contributing to the development of dementia (Kawamura et al., 1991; APA et al., 2010). Changes in the metabolism of the pancreas may result in diseases that are associated with vasculopathy such as type 1 and type 2 diabetes, whose studies show a high prevalence of dementia in diabetic patients (Garrett and Niccoli, 2022; Bortoletto and Parchem, 2023).

Inadequate blood supply due to chronic cerebral hypoperfusion results in bioenergetic deficiencies as neurons are unable to produce sufficient ATP for normal cellular functions (Hertz, 2008; Li et al., 2017).

The reduction in ATP production leads to impaired function of ATP-dependent ion channels, such as the Na^+/K^+ and Ca^{2+} pumps, generating an electrolyte imbalance. Consequently, this process increases the resting membrane potential to threshold, leading to dysregulated neuronal depolarization (Matute et al., 2002; Fann et al., 2013).

Chronic cerebral hypoperfusion triggers mitochondrial dysfunction, which compromises enzymatic activity in mitochondria, resulting in energy deficiency and vascular cognitive impairment. Furthermore, deficiency in Na^+/K^+ homeostasis has also been observed in chronic cerebral hypoperfusion, whose reduced blood flow leads to increased intracellular Na^+ concentration and decreased intracellular $K+$ concentration (Plaschke et al., 2000; Du et al., 2013; Li et al., 2017).

Excitotoxicity is triggered in chronic cerebral hypoperfusion, resulting in damage or death of neurons by uncontrolled stimulation via excitatory glutamate receptors. As neurons undergo anoxic depolarization during cerebral hypoperfusion, there is a resulting influx of Ca^{2+} ions into presynaptic neuronal terminals, culminating into a massive release of the excitatory neurotransmitter glutamate into the synaptic cleft (Li et al., 2017; Sheng et al., 2020).

Oxidative stress is induced by cerebral hypoperfusion, causing DNA damage and inducing lipid and protein oxidation that eventually results in cell death (Yamagishi et al., 2008). Elevated levels of hydrogen peroxide have been observed in brain mitochondria of rodent models, leading to vascular cognitive impairment (Du et al., 2013). Several markers of oxidative stress are elevated in patients with vascular cognitive impairment, such as lipid peroxidation and DNA oxidation, along with reduced levels of plasma antioxidant (Ryglewicz et al., 2002; Gackowski et al., 2008; Gustaw-Rothenberg et al., 2010).

Chronic inflammation has been observed in patients with vascular cognitive impairment during preclinical, clinical, and severe stages of VaD. These studies reported elevated levels of classical inflammatory mediators such as interleukin-1 beta, interleukin-6, tumor necrosis factor α and C-reactive protein. Such inflammatory mediators lead to tissue matrix degradation and peripheral immune cell infiltration, which ultimately result in various forms of cell death (Engelhart et al., 2004; Zuliani et al., 2007; Schmitz et al., 2015; Belkhelfa et al., 2018).

Studies involving brains with vascular cognitive impairment have shown the presence of reactive astrocytes and microglia in areas of surrounding lesions, along with markers of oxidation, stress, and inflammation (Tomimoto et al., 1996; Fernando et al., 2006; Simpson et al., 2007). These activated glial cells are certainly involved in the pathophysiology of vascular cognitive impairment through several mechanisms. First, they initiate and facilitate neuroinflammation, leading to cellular injury and leukocyte infiltration into the brain (Häußler et al., 2020; Marín-Teva et al., 2011). Second, inflammation suppresses the pro-survival activity of the endothelium, reducing neurotrophic neuronal signaling and leading to endothelial cell atrophy and microvascular rarefaction (Grammas, 2011; Zegeye et al., 2020).

For many patients, markers of vasculopathy coexist with the traditional features of AD, increasing the risk of dementia (Schneider et al., 2004). The relationship between AD and VaD is also confusing. VaD is a heterogeneous condition whose pathology ranges from multiple micro-infarcts to small vessel ischemic disease and microvascular injury. In some cases, the features of AD may come from a specific form of vascular injury, as a dysfunction in the blood-brain barrier that affects the transport of pAβ between the brain and the periphery and thus contribute to the deposition of parenchymal and neurovascular pAβ. Conversely, AD can cause vascular injury, such as when pAβ-induced inflammation damages the vascular endothelium. Some studies support that both hypertension and T2D increase the risk of dementia through cerebrovascular dysfunction (Sarwar et al., 2010; Gorelick et al., 2011; Cheng et al., 2012; González et al., 2022; Carvalho, Moreira, 2023).

Evidence suggests that diabetes increases the risk of AD and VaD, regardless of the age at which diabetes occurs. Thus, mechanisms of increased risk include the effects of insulin resistance, as well as increased advanced glycation end-products related to hyperglycemia

and oxidative stress, inflammation, and macro- and microvascular injury (Kloppenborg et al., 2008; Luchsinger, 2008; Strachan et al., 2008; González et al., 2022; Leibold et al., 2023).

Carotid artery occlusion results in loss of neurons in the hippocampus, impairing spatial memory (Khoshnam et al., 2018; Lee et al., 2019), increasing the levels of tumor necrosis factor α and interleukin 6, as well as increasing apoptotic cell death in the hippocampus (Khoshnam et al., 2018). One study demonstrated that two-vessel carotid artery occlusion (2-VO) reduced learning in a novel prefrontal-dependent test of object recognition, as well as it reduced the expression of synaptic markers in the prefrontal cortex of rats (Dong et al., 2018). Pathologies linked to pancreatic dysfunction, such as diabetes, lead to a greater risk of vascular occlusion, which is a necessary condition for the emergence of dementia caused by vasculopathy.

4. Discussion

This review gathered enough evidence to support our hypothesis that disorders in hepatic and pancreatic metabolism increase the risk of AD and VaD. Regardless of whether the study was in vivo, observational or experimental, the results showed that pathologies such as diabetes, chronic hepatitis, dyslipidemia, and others caused by changes in the liver and pancreas, predispose to the emergence of dementia in those affected by such diseases (Beeri and Bendlin, 2020; Dove et al., 2021; Su et al., 2023; Wee et al., 2023).

There is increasing evidence that the liver plays a key role in the etiology of dementia and cognitive impairment given its effect in glucose, insulin and mitochondrial metabolism. Besides facilitating the clearance of Aβ protein and inflammatory cytokines, the liver is the metabolic center of the body and is fundamental for the regulation of glucose/insulin metabolism as well as macronutrient metabolism (glucose, lipids and proteins) (Bassendine et al., 2020; Hunt et al., 2022). The liver is also involved in the elimination of Aβ, which is the main protein associated with AD. Studies show that about 50% of Aβ produced in the brain is eliminated peripherally, with some studies concluding that the liver is the main site for Aβ clearance (Morales et al., 2021; Hunt et al., 2022).

VaD is associated with cerebrovascular diseases and vascular risk factors, including blood pressure variability, cardiac arrhythmia, renin-angiotensin system hyperactivity, endothelial dysfunction, dyslipidemia, and T2D. Disruption of insulin signaling and glucose metabolism are key factors for inducing cerebrovascular disease and VaD (Parfenov et al., 2019; Iwagami et al., 2021).

Furthermore, a fundamental role of the liver is to convert dietary macronutrients into circulating glucose and ketone bodies, which are substrates for mitochondrial ATP production. Thus, there is a close relationship between mitochondrial function and insulin signaling. In fact, insulin resistance is known to contribute to mitochondrial dysfunction and therefore, the loss of systemic insulin sensitivity results in neuronal mitochondrial dysfunction (Schell et al., 2021). AD is associated with impaired mitochondrial oxidative phosphorylation in the brain and in many other tissues, as mitochondrial dysfunction is involved in a cascade of processes related to neurotransmitter release, oxidative stress, and dysregulated calcium homeostasis, which are all causative factors for AD (Quntanilla and Tapia-Monsalves, 2020; Abyadeh et al., 2021).

The aforementioned relationship between insulin signaling and mitochondrial function, in addition to the proven vasculopathies present in diabetic patients, corroborates the role of dysfunctional pancreas metabolism as an important risk factor for the development of AD and VaD. During homeostasis, pancreatic β-cells detect increased blood glucose levels through GLUT2-mediated glucose uptake. In response to the higher levels of intracellular glucose, β cells secrete insulin and IAPP through the constitutive secretory pathway. Both β-cell hypertrophy and the increased insulin secretion contribute to the abnormally high levels of IAPP, which results in toxic aggregation. As insulin secretion increases with hyperglycemia in diabetic and prediabetic patients, there is also a simultaneous increase in IAPP secretion. IAPP is prone to aggregation, which means that increasing IAPP levels can lead to the formation of toxic oligomers in the pancreas, similar to other amyloidogenic peptides such as Aβ. Other previous reports have also demonstrated that IAPP can negatively affect kidney, muscles and blood pressure (Neutzsky-Wulff et al., 2012; Mukherjee et al., 2017). IAPP can bind to receptors in the kidneys, and a small study in humans found that systemic infusion of IAPP led to increased plasma renin levels, suggesting that IAPP may induce hypertension, which is a risk factor for VaD (Germanos et al., 2021; Bortoletto and Parchem, 2023).

Therefore, this current review is important for alerting the scientific community that dysfunctions in the liver and pancreas have a high potential to trigger pathologies that considerably increase the risk of developing AD and vascular dementia. The evidence found and presented in this review allows us to recommend that the metabolism of both organs needs to remain at a physiological standard as a way to prevent hyperglycemia, dyslipidemia, vasculopathies, and other risk factors for the main forms of dementia. However, as this is a narrative review of the literature, the main limitation is that there is no high level of evidence to support a causal relationship between disturbances in hepatopancreatic metabolism and dementia.

5. Conclusion

The homeostasis of glucose, insulin, lipid production, cortisol and other substances metabolized in the liver and pancreas is essential, due to the fact that disturbance in the metabolism of such substances may generate pathologies capable of causing brain changes that might result in Alzheimer's disease and vascular dementia. The maintenance of a healthy glucose metabolism in the brain should be a priority focus of AD and VaD prevention, as it seems to be a viable strategy of preserving cognitive resilience and ameliorating dementia progression.

Dietary energy and macronutrient intake have shown to influence the levels of hepatic proteins involved in protein, lipid, and carbohydrate metabolism. Nutrition has a profound impact on aging and age-related diseases, such as dementia, and new clinical trials are important to prove the effectiveness of nutritional interventions in contributing to the physiological functioning of the liver and pancreas as well as in the prevention of dementia.

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Declaration of Competing Interest

The authors declare no conflict of interest, financial or otherwise.

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