Alzheimer Disease and Type 2 Diabetes Mellitus: The Link to Tyrosine Hydroxylase and Probable Nutritional Strategies

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Abstract: Alzheimer disease (AD) and type 2 diabetes mellitus (T2DM) are chronic health disorders that affect millions of people around the world. According to recent studies, there are molecular similarities in the inflammatory pathways involved in both AD and T2DM, which opens a new avenue for researchers with different perspectives to target the cause of these diseases rather than their obvious symptoms. Several links between inflammation, cardiovascular disease, T2DM and central nervous system disorders such as AD and Parkinson's disease have been elucidated. Mutations in the hippocampal-β-amyloid precursor protein gene in genetically high-risk individuals have been shown to cause the early onset of AD symptoms. The overexpression of β-amyloid protein in the hippocampal region and the synaptotoxicity that occurs as a result have been considered a typical feature of AD and leads to neuronal loss and cognitive decline. However, the identity of the cellular components that cause the late onset of the disease seen in the majority of the cases is still unknown. Synaptic insults associated with neuronal dysfunction may involve several cascades and molecules, one of which has been hypothesized to be tyrosine hydroxylase (TH). The axons of the noradrenergic cells that project to the hippocampus appear to be affected by the β-amyloid protein, which subsequently contributes to TH loss in Alzheimer brain cells. In this review, we attempt to shed light on the important mechanisms involved in AD as well as T2DM such as inflammatory factors, abnormalities in the insulin signaling system and the possible role of the endocrine enzyme TH.

Keywords: Alzheimer disease, type 2 diabetes mellitus, tyrosine hydroxylase, nutritional strategies.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common metabolic diseases, the prevalence of which increases with age. Diabetes is commonly reported in more than 12% of the adult population in the Middle East and North Africa, with a global occurrence of 8.3% among adults between 20 and 79 years old [1]. T2DM is a heterogeneous, multifactorial polygenic disorder that is characterized by an insulin defect, including in its action (insulin resistance) and secretion (due to a beta cell secretory defect). Evidence has suggested a possible link between T2DM and mitochondrial gene mutations [2]. It has been reported that the expression of the peroxisome proliferator-activated receptor gamma co-activator 1-alpha gene is down-regulated, which is responsible for oxidative phosphorylation in diabetes [3]. T2DM has also been identified as a risk factor for Alzheimer disease (AD) [4], a progressive neurodegenerative disorder (ND) of unknown etiology that progressively leads to severe incapacitation and ultimately death [5]. Although T2DM increases the likelihood of AD, the exact mechanisms responsible for this link remain unclear. Recent research has shown that there are several similarities between T2DM and AD [6]. Common physiological processes that underlie both diseases include systemic inflammatory conditions, atherosclerosis, oxidative stress, progressive amyloidosis and other ageing-related processes [7]. Metabolic syndrome, T2DM and AD are systemic inflammatory conditions associated with elevated levels of circulating acute phase inflammatory markers such as C-reactive protein, which indicates insulin resistance as well as contributes to the development of T2DM and AD [8-10]. Moreover, elevated levels of butyrylcholinesterase may act as a key triggering factor for the initiation of the inflammatory processes observed in T2DM and AD *via* the down-regulation of the 'cholinergic anti-inflammatory pathway' [11]. AD has been implicated in cholinergic system dysfunction when there is

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an active loss of choline acetyltransferase, thereby leading to cognitive decline [12, 13]. Cholinergic neurons in the basal forebrain release acetylcholine (ACh), which binds to two receptor subtypes [muscarinic ACh receptors and nicotinic ACh receptors], the numbers of which are also significantly reduced in AD brains [14]. The M1 receptor is a subtype of the muscarinic ACh receptors that is involved in cognition and postsynaptic transmission. Its coupling with nucleotide-binding G-proteins is reduced in AD subjects with severe dementia [15]. The reduced coupling was reported to be proportional to the activity of protein kinase C, as well as the density of N-methyl-D-aspartate receptors in the frontal cortex of AD subjects [16].

Evidence for the association of vascular risk factors such as T2DM, hypertension, obesity and dyslipidemia with dementia has been systematically reviewed by Kloppenborg *et al.* using longitudinal population-based studies [17]. This review also found that at midlife, the population at risk for dementia was also the one most likely to have hypertension, with up to 30% of hypertensive cases presenting with late-life dementia. Later in life, diabetes appears to be the greatest risk factor for dementia. Hence, new comprehensive research aimed towards understanding the coexistence of T2DM and AD will assist in understanding the pathophysiological similarities between these two disorders. T2DM and impaired fasting glucose have also been linked to an increased risk of mild cognitive impairment [18], a significant risk factor for dementia. The complications of T2DM (heart disease, stroke, neuropathy, blindness and kidney disease) are likely to be exacerbated by insulin resistance, as well as by hyperglycemia. Because the incidence of diabetes is on the rise worldwide, the chances of a pre-diabetic person developing these serious health problems have increased, regardless of whether they eventually develop T2DM [19]. Pre-diabetes is a condition of impaired fasting glucose or impaired glucose tolerance in which the blood glucose levels are not high enough for a person to be categorized as diabetic but are still higher than normal, causing insulin levels to rise years before abnormalities in blood sugar develop. This is a condition that can be maintained and controlled [18].

It is likely that neurofibrillary tangles are formed as a result of the neurodegeneration of islets that takes place in T2DM, which occurs similarly with AD. Although the embryologic development of the pancreas is endodermal in origin, the pancreas is highly innervated and exhibits many similarities with the brain at the molecular level of the transcriptome and proteome. Its initial development takes place in accordance with notochord signals and later utilizes similar transcription factors, such as Nkx2.2 (Homo sapiens NK2 homebox2), Nkx6.1 (Homo sapiens NK6 homebox1), NeuroD (Homo sapiens neurogenic differentiation), Neurogenin3 (Homo sapiens neurogenin 3) and Pax6 (Homo sapiens paired box6), which are critical for the development of the central nervous system (CNS) [20]. Studies of cognitive changes in diabetes have shown that they may be mediated by fluctuations in glucocorticoid levels [21]. Increases in glucocorticoid levels have been demonstrated to be neurotoxic, causing synaptic loss in the hippocampus [22]. Atrophy of the hippocampus leads to cognitive impairment, especially in the elderly [23]. Increased hypothalamic-pituitary-adrenal axis activity in AD markedly increases cortisol levels, condition also known as AD-induced hippocampal degeneration [24].

A BRIEF INSIGHT INTO AD

Due to improvement in preventive, diagnostic and medical treatment for various diseases in the modern era, the average age of people in most industrialized countries continues to progressively increase over time. With this increase, there is also a rise in the incidence of ND such as AD, which is a common health problem faced by the elderly population in developed countries and puts huge strains on both social and healthcare budgets worldwide [25]. Epidemiological surveys reported that the worldwide incidence of dementia is 24.3 million cases, with 4.6 million new cases reported each year. The total figure is estimated to reach 80.1 million by 2040. However, the rate of increase in the incidence of dementia is 3 to 4 times higher in developing countries than in developed countries. As a result, it is predicted that by 2040, 71% of all dementia cases will be in developing countries [26, 27]. In the case of AD, neural dysfunction in the brain is induced by numerous biological cascades, which lead to the classic pathological hallmarks of the disease. The biological changes are characterized by the presence of (i) extra-neuronal amyloid deposits that contain the small, toxic cleavage product of amyloid precursor protein processing, (ii) intraneuronal neurofibrillary tangles comprised of hyperphosphorylated tau and (iii) synaptic loss. Of the neurotransmitters involved, the cholinergic system is the earliest and maximally affected, therefore it receives the greatest attention with regard to drug design and development due to its pivotal role in learning and memory processes. Protein misfolding is said to play an important role in both AD and T2DM, as does the aggregation of amyloid peptides and hyper-phosphorylated proteins (Fig. **1**).

LOW-GRADE SYSTEMIC INFLAMMATION: A PHENOMENON COMMON TO BOTH AD AND T2DM

Changes in human behavior and lifestyle over the last century have resulted in burgeoning rates of obesity and metabolic syndrome, leading to a dramatic increase in the prevalence of T2DM. It has been reported that more than 18 million Americans are primarily suffering from T2DM. In Australia, the prevalence of T2DM is slightly lower, perhaps due to a healthier lifestyle that is more active and incorporates frequent outdoor activities. Adipose tissues are the known storage site of energy in the form of lipids. Products of adipose tissue such as adipokines appear to function beyond merely serving as energy storage and also influence the homeostatic mechanisms involved in the link between obesity, insulin resistance and inflammatory disorders [28]. Visceral fat and macrophages secrete adipokines, which induce lipid toxicity. This toxicity then leads to oxidative stress and damage to the blood brain barrier and triggers the formation of amyloid beta protein [29]. Although leptin and adiponectin levels do not differ between normal and AD subjects, the presence of APO lipoprotein E (ApoE) is a risk factor [30].

Pathologically, excess abdominal adipose tissue increases the release of free fatty acids, which directly affects insulin signaling, diminishes glucose uptake in the muscle, drives exaggerated triglyceride synthesis and induces gluconeogenesis in the liver. Recently, experimental and

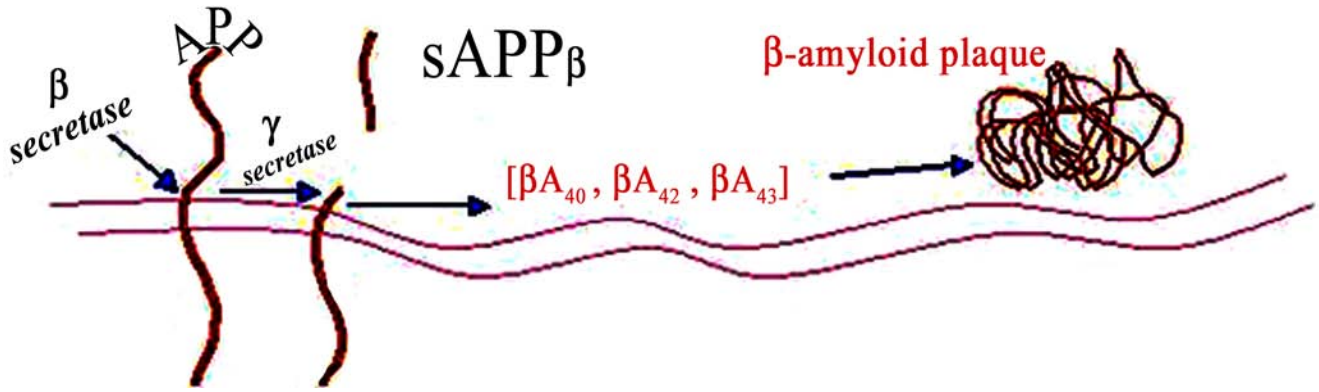

Fig. (1). Illustration of abnormal protein processing in AD. (APP, amyloid precursor protein; βA, β-amyloid).

clinical studies have shown the existence of pathways leading from obesity to the manifestation of diabetes through a variety of fat-derived proteins termed "***adipokines***". Adipokines also include various other proteins such as tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), interleukin 6 (IL-6), plasminogen activator inhibitor-1 and monocyte chemoattractant protein-1 [9]. The adipokines released by either adipocytes or adipose tissues are believed to act as a substrate for obesity-related complications such as T2DM and atherosclerosis [31, 32]. The adipokines identified to date, such as adiponectin, leptin, resistin and retinol binding protein 4, function as modulators of glucose and lipid metabolism. They can also act as inflammatory markers, as is the case with TNF-α, IL-6, plasminogen activator inhibitor-1 and monocyte chemoattractant protein-1, among others [9]. The deleterious effects of adipokines and adipotoxicity include the downregulation of insulin's action on its target tissues (muscle, liver and adipose tissues) and the promotion of inflammatory processes, which leads to systemic insulin resistance, apoptosis in pancreatic ß cells and atherosclerosis [33]. Moreover, several transcription factors and kinases such as c-Jun N-terminal kinase and the inhibitor of kappa B kinase–beta (a kinase located proximal to nuclear factor-κB that participates in inflammation), lead to downregulation of the insulin signaling pathway and functional impairment and apoptosis of pancreatic β -cells [34]. Thus, these inflammatory cytokines, adipokines and transcription factors result in hyperglycemia, which is the biochemical hallmark of T2DM. Furthermore, an inflammatory response has also been reported to be involved in atherosclerosis, which leads to diabetic cardiovascular complications, stroke and AD [35]. Insulin plays an important role in the functioning of several biological systems in our body, thus disruption of its functions can cause several uncontrollable negative biological cascades, which take the form of mis-signaling towards its receptor proteins at various cells, including those affecting neurons.

An earlier study revealed that the systemic injection of IL-1 can reduce extracellular ACh in the hippocampus, indicating that an increased level of IL-1 could be involved in AD by lowering cerebral ACh levels [36]. The association between AD and inflammation has been previously corroborated by Gupta *et al*. [37] using evidence based on the increase of plasma and cerebrospinal fluid levels of inflammatory cytokines such as IL-1, IL-6 and TNF-α in patients with AD [38-40]. The involvement of an inflammatory process in AD is further supported by the observation that inhibition or neutralization of the actions of TNF-α as well as other inflammatory cytokines are of benefit to patients with AD [41, 42]. According to new research findings, AD and T2DM seem to be related in that they are both systemic inflammatory conditions that can be ameliorated by normalizing common pathways associated with systemic inflammation. Changes in the levels of some inflammatory markers such as C-reactive protein, TNF-α, IL-6 and lipid peroxides are common to both T2DM and AD, suggesting that a close association exists between these common and progressive diseases. These findings suggest that low-grade systemic inflammation is an underlying thread in the comorbidity of T2DM and AD. However, the factors that trigger the inflammatory process in these diseases remain unclear.

The administration of insulin or even oral hypoglycemic agents may increase ACh levels in the brain, particularly in the hippocampus up to some extent with respect to specific doses. Beyond that critical concentration of insulin, no further increase in ACh level may occur, however further increase in insulin amount can cause adverse affect on ACh level reduce it. Accordingly, such drugs could display interesting neuroprotective effects because AD is also influenced by factors that affect insulin resistance. Impaired glucose tolerance is associated with impaired cognition independent of age, and there are reports of an increased risk of AD with diabetes [43, 44]. The relationship between diabetes and AD is complex and remains to be fully elucidated. Although the localization and pathological features of diabetes and AD differ markedly, there are several similarities. Many researchers believe that both AD and T2DM are chronic progressive conditions even before a diagnosis is made or treatment instigated. Unquestionably, hyperglycemia may induce oxidative stress as well as the glycosylation of key regulatory proteins, which potentially results in their malfunction; however, in both diseases, many additional interactions exist and appear to be facilitated at the level of insulin and its degradation enzyme. In this regard, insulin receptors are localized throughout the brain, with particularly dense distributions detected in the hippocampus, entorhinal cortex and hypothalamic regions [45].

THE ROLE OF THE HYPOTHALAMUS IN FEEDING BEHAVIORS

The hypothalamus is responsible for neural signals related to the storage of fat, balance of energy and satiety. Energy storage and expenditure is also regulated by the hypothalamus *via* the autonomic nervous system. Although insulin is not synthesized in the CNS, the CNS is the major site of the expression of insulin receptors. The majority of insulin receptors are present in the hypothalamus, olfactory bulb, hippocampus and throughout the limbic system [46]. In normal healthy adults, insulin levels in the CNS correlate with levels in the blood. Insulin levels are disturbed in obese subjects, leading to reduced insulin levels in the CNS. Therefore, a lesser amount of insulin is available for satiety signaling, exposing a person to CNS insulin resistance [47]. Fat storage is more efficient in mice deficient in the Ubiquitin *b* gene, and deletion of this gene is elemental in neurodegeneration within the hypothalamus. There appears to be a strong correlation between the lack of Ubiquitin genes, especially Ubiquitin *b*, and adult-onset obesity due to neuronal loss, suggesting a larger role of Ubiquitin *b* transcription in the neuronal dysfunctions that occur in neurodegeneration [48].

THE ROLE OF PERIPHERAL AND CENTRAL INSULIN-RESISTANCE IN T2DM AND COGNITIVE DECLINE

AD and dementia are both age-related brain disorders that involve the loss of memory [49]. Although all dementias cause damage to the cerebral cortex, a few only disrupt certain regions of the cortex, making these forms reversible. AD, however, is an irreversible progressive brain disease, and patients display symptoms that are likely precipitated by a combination of factors, such as genetic, environmental and lifestyle. In some studies, only memory seems to be affected by diabetes-related factors [50]. Additionally, the amount of time elapsed since the first diagnosis of T2DM is important for AD because it is a probable risk factor for increased cognitive decline with age [51]. Areosa and Grimley suggested that the duration of insulin exposure correlates with the severity of T2DM [52]. One of the major contributors to the progression to hyperglycemia and T2DM is the resistance of peripheral cells such as fat, muscle and liver cells to the stimulatory effects of insulin. Many studies have suggested that the risk of cognitive decline and neurodegeneration is increased in insulin-resistant patients who are in pre-diabetic states [18, 50], indicating that both the loss of the action of insulin and the hyperglycemic condition are equally important for the manifestation of the disease. Because insulin resistance can be detected in the cortex and hippocampal regions, it is possible that insulin resistance in these parts of the brain also contributes to T2DM-related dementia. Experiments conducted by Ho *et al.* [53] suggest that in a genetic background already predisposed to AD, diet-induced peripheral insulin resistance during pre-diabetic states promotes neuronal insulin resistance and exacerbates the molecular pathology of AD. Insulin has been reported to shield retinal neurons from toxin- and stress-induced apoptosis *via* several different pathways [54, 55]. Insulin resistance in T2DM may therefore render neurons more susceptible to neurotoxic insults (e.g., β-amyloid in AD), resulting in reduced neuronal viability in dementia-affected neurodegenerative areas of the brain. T2DM and/or impaired glucose tolerance can develop for various reasons, such as increased retinol binding protein and monocyte chemo attractant protein-1 levels. In these disorders, the muscle, adipose tissue and liver become less responsive or resistant to the action of insulin, thereby creating an insulin-resistant condition. The molecular-pathology of insulin resistance could be understood through the conduction of a comparative study of the normal and abnormal kinetic status of insulin receptors, substrates, and their signaling pathways.

The early onset of AD is related to a single mutation of the ApoE gene located on chromosome 19. Apo lipoprotein E has several different isoforms, with Apo lipoprotein E 2, 3 and 4 occurring more frequently. Increased insulin resistance may result in the absence of the Apo lipoprotein E 4 allele, as reported by Craft *et al.* [56]. This could mean that the modulation of memory in AD patients may be possible by increasing insulin activity. Insulin may have a vital role in normal memory processes and has been clearly implicated in memory function in AD [56]. Insulin has also been reported to have a regulatory action on both β-amyloid and its precursor protein [57] and may regulate *tau* phosphorylation [58]. A recent report indicated that a peptide mimic of amylin blocked the cytotoxicity of β-amyloid, suggesting a molecular link between the related systemic inflammatory conditions of AD and T2DM [59]. The protein *tau* is phosphorylated by the glycogen synthase kinase 3 (GSK3), which has been implicated in the link between T2DM and AD [60]. Furthermore, animal experiments have shown that two isoforms, GSK3α and GSK3β, are involved in neuroprotection, and the down-regulation of GSK3β seems to have a common neuroprotective function [61, 62].

LINK BETWEEN TYROSINE HYDROXYLASE AND T2DM IN ND

The four members of the aromatic amino acid hydroxylase family, phenylalanine hydroxylase, tyrosine hydroxylase (TH), tryptophan hydroxylase (TPH) 1 and TPH 2, share a similar organization of their three-dimensional structure and mechanisms of action. Of these, TH and TPH are involved in the neuroendocrine system and affect the rate-limiting steps involved in the synthesis of neurotransmitters and hormones, including catecholamine, serotonin and melatonin. TH is primarily present and active in the brain and cytosol, although small amounts have also been reported in membranes. Its presence in the sympathetic and CNS tissues of mammalian systems is diverse, but it is found primarily in the brain, adrenal medulla and peripheral sympathetic neurons [63]. Mutations in the TH and TPH genes have been implicated in neurological disorders such as Parkinson's, AD and some forms of dystonia. Catecholamines have also been implicated in cognition and other related processes such as behavior, mood states or even learning [64]. Diabetic nephropathy involving a dysfunction of the renal glomerulus is known to interfere with catecholamine biosynthesis. A disruption of the synthesizing and degradation enzymes of catecholamine synthesis has been observed in acute and chronic complications of T2DM [65].

STRUCTURE AND MOLECULAR GENETICS OF THE TH GENE

Tyrosine hydroxylase is an oligomeric protein of four identical sub-units, making it a symmetric tetramer that can be further differentiated into three different domains: the N-terminal regulatory domain of 156 residues, the central catalytic domain with approximately 297 residues and the C-terminal oligomerization domain containing 44 residues [66]. The kinetic activity and/or binding of TH to its protein partners is controlled by its compact structure, which creates four to five phosphorylation sites at the N-terminal end [67]. The physiological significance and mechanism of TH phosphorylation have yet to be fully understood [68]. Two elements, the TH promoter and the TH fat-specific element, contribute to the regulation of the TH gene [69]. Both have been found to independently regulate the functioning of the gene. When regulating TH gene transcription, the cyclic AMP response element binds to the cellular transcription factor cyclic AMP response element binding-protein (CREB) and the co-activator CREB binding protein (CBP), while the Fos–Jun (cellular proto-oncogene) complex binds to the TH fat-specific element. Immunohistochemistry of both these elements have shown that they act independently in the dopaminergic regions, mid-brain and olfactory bulb of the brain, thereby regulating the TH gene according to tissue type.

The human TH gene localizes to chromosome 11p15.5 [70], spans approximately 8 kilobases and contains 14 codifying exons. There are four different isoforms of the human TH gene, h-TH1-4, and although they share similar kinetic properties, they are expressed in varying amounts within the same tissues. For example, h-TH1 is the more abundant and active form of the gene [71]. The insulin-like growth factor II gene cluster on the 11p chromosomal locus of the TH gene has been shown to be a possible locus for diabetes mellitus, although it has also been implicated in certain bipolar disorders. Three single nucleotide polymorphisms, Val81Met, Leu205Pro and Val468Met, as well as the tetra nucleotide repeats in the first intron, appear to be critical in the modification of enzyme activity [72].

Earlier reports have indicated that individual gene polymorphisms are not only differentially distributed among different ethnic populations but can also have different associations with disorders such as depressive disorder or metabolic syndrome. However, larger studies of the polymorphisms found within specific populations are needed to validate these studies [73]. Microsatellite polymorphisms of the TH gene that lead to disturbances in the TH and insulin variable number of tandem repeat (INS –VNTR) genes have been found to have strong links with insulin resistance in depressive disorders [74].

TH - MODULATION IN AD

The sympathetic nervous system relies on catecholamines, which also play the role of neurotransmitters in the CNS. The hydroxylation of L-tyrosine to L-dopa is of prime importance in the formation of these catecholamines [75]. The enzymatic action of TH leads to the synthesis of dopamine and noradrenaline (Fig. **2**). Several studies have reported positive associations between TH and bipolar affective disorder [76], and animal experiments indicate that the biochemical activation of TH results in the simultaneous trigger of neurobiological changes, resulting in behavioral problems like depression [77]. The accumulation of β -amyloid and the hyper-phosphorylation of *tau* protein are factors that lead to insulin resistance in the brain. Therefore, conditions of chronic stress and hypercortisolemia can result in AD. AD is thus often characterized by prior depression [78]. It has been observed that, apart from TH, the protein *O*-carboxymethyltransferase is also present in anatomically similar catecholamine-rich regions of the brain. It would therefore be possible that the protein *O*-carboxylmethyl-transferase also plays a role in the modulation of catecholaminergic neurotransmission [79].

BRAIN DEVELOPMENT AND FUNCTIONING IN RELATION TO TH

In adult mammalian brains, a slow neuronal regression develops, resulting in gradual brain atrophy. This causes changes in the mRNA and protein concentrations of TH. It has been reported that similar mechanisms that result in potential changes in TH protein could be triggered in AD [80]. A very interesting observation by Katori *et al.* [81] showed that TH immunoreactive cells transiently appear in the midline epithelial seam during the palatal fusion that occurs in the 9^{th} week. These TH immunoreactive cells were later found to disappear in 15-week-old fetuses, suggesting a greater and novel role of TH, not only for proper brain functioning but also during development. Studies conducted during brain cortical development at approximately 9-14 gestational weeks have indicated that the TH gene is not expressed until it is induced by brain-derived neurotrophic factor, dopamine or both (independently). This could explain the necessity of a long gestational age, during which induction of the TH gene takes place [82]. The mature brain expresses TH in the hypothalamus, midbrain, brainstem and olfactory bulb. TH is also known to be expressed in the periphery of the sympathetic ganglia, paraganglia and chromaffin cells [83]. Brain function under normal or patho-physiologically degenerative conditions involves a small presynaptic protein called alpha synuclein. This protein has been implicated in the regulation of dopaminergic neurotransmission. Its interference with the cyclic AMP-mediated signaling of TH in the cells of Parkinson's disease patients indicates that this small protein has a greater role to play in AD [84]. This hypothesis, however, needs to be further studied and evaluated. In mammalian systems, mRNA for TH contains four isoforms that are inequitably distributed between catecholaminergic neurons and the terminal fields of catecholaminergic cell populations. The relative distribution of these isoforms in normal and neurodegenerative conditions may shed light on the specific role of each isoform in the expression of dopamine [85].

THE ROLE OF COFACTOR TETRAHYDROBIO-PTERIN IN THE EXPRESSION OF TH ACTIVITY

Tetrahydrobiopterin (BH4) is a cofactor required by several enzymes such as TH, TPH, phenylalanine hydroxylase and nitric oxide synthase. Because the activity

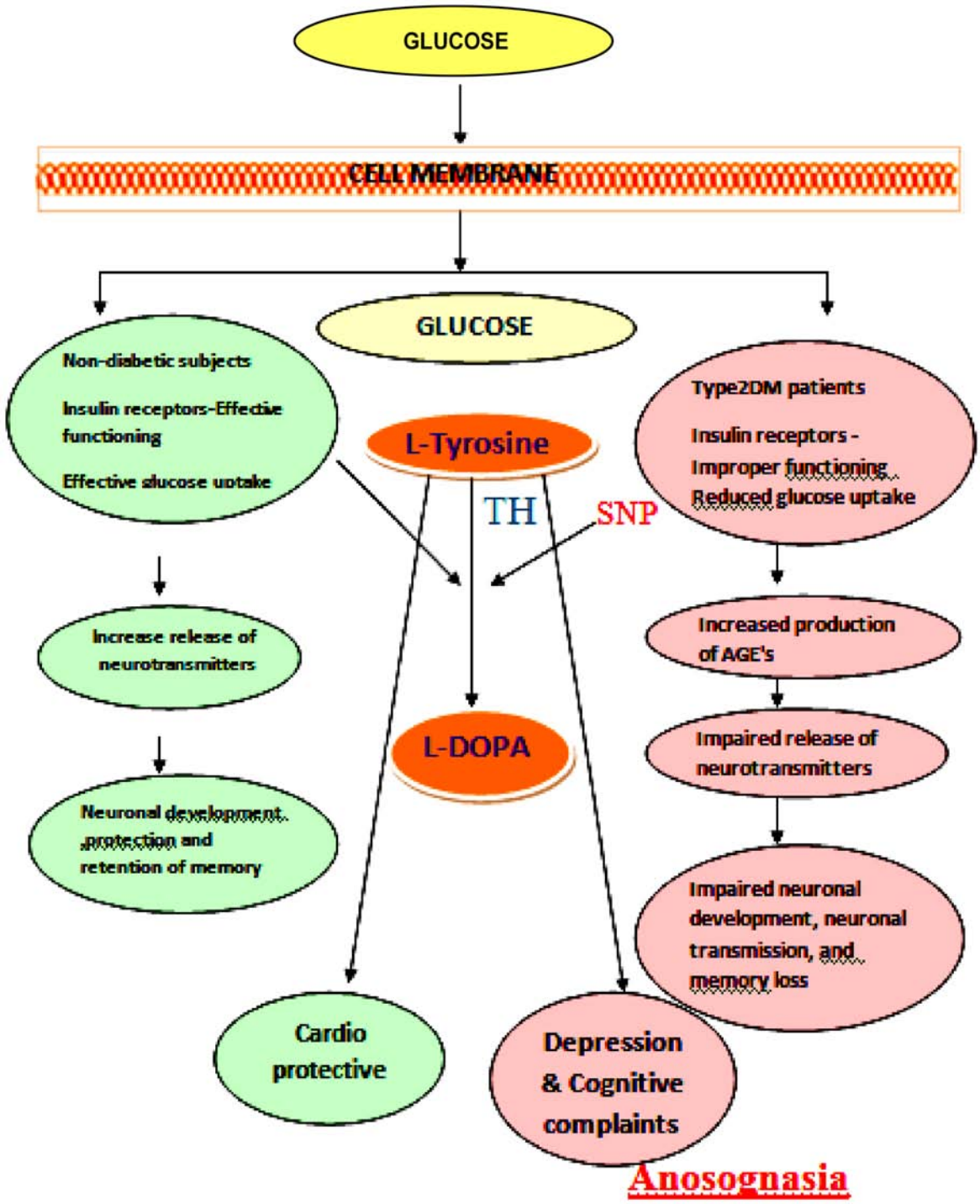

Fig. (2). Tyrosine hydroxylase (TH) affects the rate-limiting step of the conversion of L-Tyrosine to L-Dopamine. The TH gene, which is located on locus 11p 15.5, exhibits a single nucleotide polymorphism (SNP) in T2DM due to the production of advanced glycated end products, which leads to depression, one of the prime symptoms of AD.

of BH4 largely relies on the activity of GTP cyclohydroxylase 1 enzyme, BH4 may also indirectly regulate the activity of TH, and a slight change in the level of the cofactor could lead to depressive symptoms in predisposed individuals, as well as further implicate the heterocyclic amines [86]. New theories do not attribute the ineffectiveness of TH completely to the BH4 cofactor during all stages of development. For example, the cholinergic differentiation factor derived from mouse sweat glands can suppress the characteristics of the noradrenergic phenotype during development through the inhibition of BH4. However, during the developmental stage, the expression of GTP cyclohydroxylase 1 has been shown to be independent of TH activity [87].

NUTRITIONAL STRATEGIES TOWARDS THE ALLEVIATION OF THE SYMPTOMS OF AD

Recently, complementary therapies have been gaining momentum and acceptance by the general public. Nutritional therapies offer an alternative approach for the alleviation of the symptoms associated with AD. Food has a large impact in alleviating the common complications of the disease, making one wonder if there are many other factors that also contribute to the etiology of this disease. Standard healthy lifestyle advice targeted for general public can take an added relevance of importance when practical prevention measures of AD are included. Furthermore, the widespread nature of cognitive problems and memory deficits makes recognizing the need for and adoption of an appropriate nutritional strategy treatment quite challenging. Many nutrients from across the globe have been identified as helpful in treating the symptoms of AD and offer relief to the patients. Here we list a few of the most researched and well-studied of the nutrients used. A study that administered a western diet to animal models showcased the increased cerebral oxidative stress and declining cognitive performance that occurs in the aged brain due to a high fat diet (60% fat). Our cells protect themselves against free radicals and other reactive substances by means of a group of enzymes and radical scavengers called the nuclear factor 2 (Nrf2) system [88]. Reduced Nrf2 activity has been found in cases of oxidative damage, implying a diminished antioxidant response with a high fat diet.

BENEFICIAL EFFECTS OF THE MEDITERRANEAN DIET AND AD

Traditionally, a diet low in animal fats and rich in vegetables, red wine and olive oil (a monounsaturated fat) has been referred to as the Mediterranean diet. People who adopt this type of diet have a lower risk of developing many diseases (Fig. **3**). Many studies have shown a beneficial link between a Mediterranean diet and cognitive function, dementia and AD [89, 90]. Scientific studies by Greek researchers have enumerated the implications for T2DM, cardiac problems and obesity. Metabolic disorders comprise all three symptoms, which could, in turn, have an implication for ND. A recent meta-analysis by Sofi *et al.* [91] that used a large number of subjects authenticated the protective benefits of a Mediterranean diet against ND. Experts believe that the antioxidant and anti-inflammatory benefits of the foods associated with the diet confer health benefits against a variety of diseases. A new analysis that pooled the findings from 50 different studies involving more than 500,000 patients [92] found that the Mediterranean diet has beneficial effects against metabolic syndrome, which comprises the five components of a pre-diabetic condition. The researchers reported that adherence to a Mediterranean diet was also associated with a 31% reduction in the risk of developing the syndrome.

OTHER NUTRIENTS ALLEVIATING AD SYMPTOMS

Omega-3 fatty acids, one of the most essential fatty acids, seem to play a significant role in the alleviation of AD symptoms, although the underlying mechanism needs to be elucidated further. Docosahexaenoic acid has been shown to improve cerebrovascular function and cognition and exhibits neuroprotective qualities [93]. Transgenic mice that mimic AD-like pathology show a considerable reduction in cortical β-amyloid levels, although more detailed analysis is necessary to determine the potential pathways that are involved in these beneficiary effects [94]. It has been hypothesized that the anti-inflammatory effects of docosahexaenoic acid most likely contribute to the down-regulation of the amyloid precursor protein activity that is considered destructive for neurons. Furthermore, a reduction in the incidence of ischemic stroke in AD patients consuming docosahexaenoic acid *via* fish oil has also been demonstrated [95, 96]. Moreover, it has been well established that AD is a disorder in which oxidative stress [97] is increased, leading to the continuous generation of free radicals that promote cell damage and apoptosis, further supporting the beneficial role of antioxidants in alleviating AD-associated symptoms [98, 99]. Antioxidants such as β-carotene, anthocyanins, genisten, hops extract, policosanol, sesamin, vitamin D, flavanoids and folates [100-102] may inhibit the accelerated production of β-amyloids, which has been shown to increase damage to neurons. Cinnamon extract [103] and chromium picolonate [104], which have been reported to curb insulin resistance, may also be beneficial in preventing neuronal apoptosis. Coenzyme Q10, lipoic acid, creatine and caffeine have also been shown to contain neuroprotective effects in animal studies [105]. In general, some nutraceuticals exhibit neuroprotective activity because they increase antioxidant defense mechanisms, thereby reducing the release of free radicals and retarding neuronal apoptosis [99, 106, 107]. A safer and more convenient method is the molecular approach, which involves a combination of nutrients that protect neural function. This approach could pave the way to a further holistic therapeutic approach. Safer nutrient therapies could also be used as preventive measures in patients who are genetically at-risk and also in patients at the start of cognitive decline [108, 109].

CONCLUSION AND PERSPECTIVES

The studies listed in this review support a link between AD and T2DM. The action of TH appears to be quite intriguing, resulting in speculation about the role of different enzymes in the development of AD and its link with T2DM. The apparent consequences of neurochemical changes during age-related anorexia are well known, such as declines in food intake and body weight. This is especially the case in advanced stages within both humans and laboratory animals, but micro-level mysteries remain puzzling, such as the modulation of the non-neuronal cholinergic system in the peripheral blood of AD patients. The expression of insulin seems to be modulatory in the progression of neurodegeneration in AD. More general physiological processes, such as angiopathic and cytotoxic developments and the induction of apoptosis or non-apoptotic cell death *via* the production of free radicals, greatly influence the progression of AD and T2DM.

T2DM and depressive disorders such as AD seem to be governed by mechanisms that are both physiological and

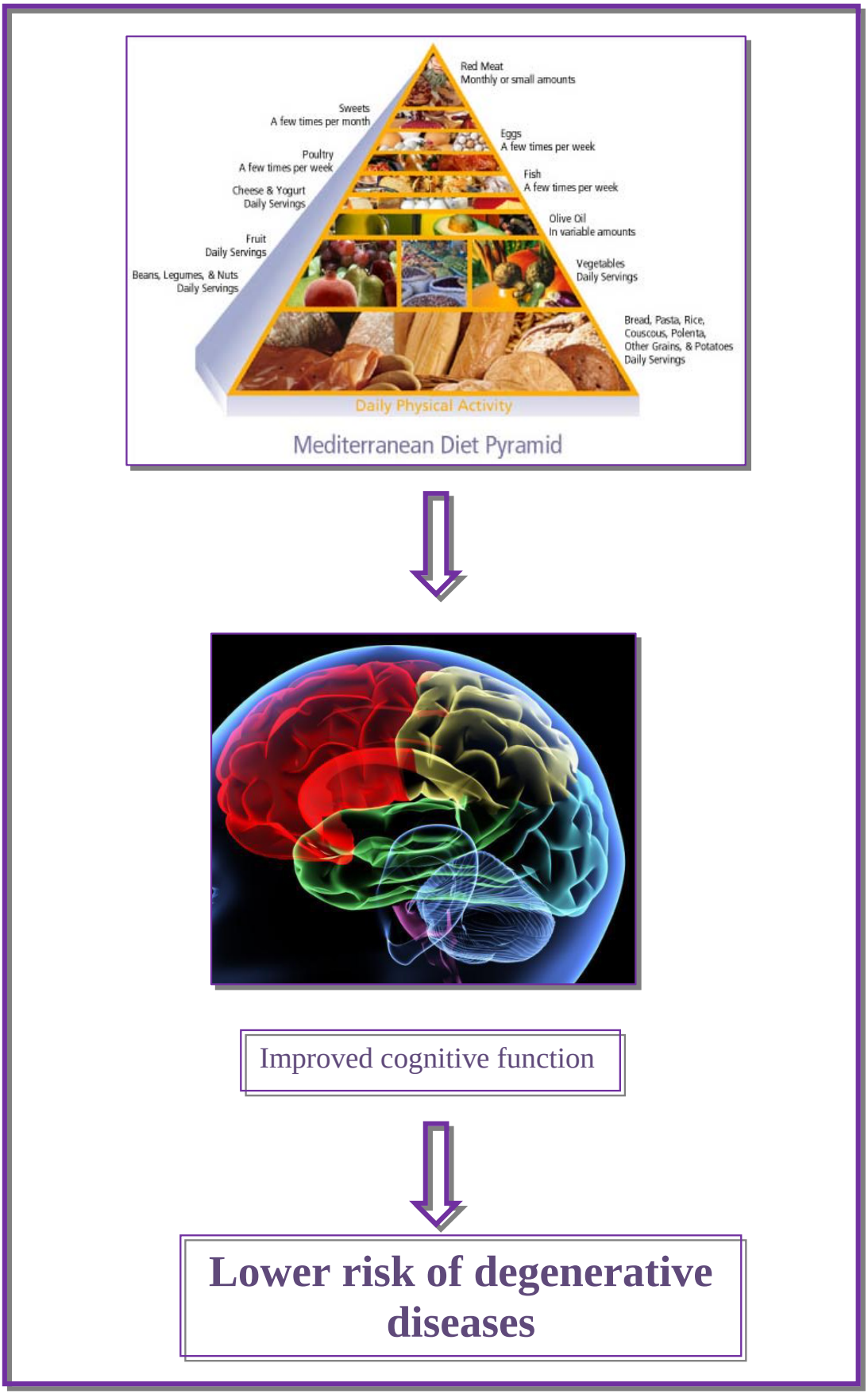

Fig. (3). Potential positive effect of the Mediterranean diet on cognitive function and degenerative diseases such as AD and dementia [112,113].

behavioral in nature. As a result, Palinkas *et al*. suggested that elderly persons exhibiting depressive symptoms should be treated for depressive disorders even if they do not meet the Diagnostic and Statistical Manual of Mental Disorders criteria, to help prevent them from acquiring T2DM [110]. Most AD patients exhibit serious aggressive behavioral problems, some of whom also have significantly higher levels of alpha-2 adrenergic receptors in the cerebral cortex. It has been reported that among individuals with AD, those who exhibit aggression are more likely to exhibit elevated levels of these receptors than individuals without similar aggressive behavior [111]. A recent study has indicated that individuals who exhibit thinning of the cerebellar cortex, as measured by magnetic resonance imaging, stand a greater risk of developing AD than those with a cerebellar cortex of normal thickness [112].

It has been observed that nutritional support is essential for normal homeostatic mechanisms. Nutrition also plays a role in the development of proper cognitive function and neuronal plasticity. Obesity, an increasingly prevalent nutritional disorder, is alarming to the scientific community, who wish to better understand its mechanisms and role in brain aging and age-related neurodegeneration. It is already evident from clinical and rodent studies that diet-induced metabolic disturbances can lead to dementia. Further studies on these links can reveal the complexity of brain function with respect to brain pathology. Another area of concern that needs to be addressed is maternal obesity, which may predispose offspring to obesity and increase neuronal modulations [113]. Further research in this field will open new avenues towards understanding the common physiological characteristics of AD and T2DM *via* their links to TH and will be helpful in the development of proper treatments for various disorders. Diet-induced neuronal imbalances due to obesity and the strategic treatment of these conditions with proper nutrition is a field that needs to be investigated. The role of diet and metabolic disturbances in modulating aging disorders could be targeted in the development and implementation of possible nutritional strategies involved in the alleviation of AD and T2DM.

LIST OF ABBREVIATIONS

ACh	=	Acetylcholine
AD	=	Alzheimer disease
ApoE	=	Apolipoprotein E
CNS	=	Central nervous system
IL-1	=	interleukin 1
IL-6	=	interleukin 6
ND	=	neurodegenerative disorder
BH4	=	Tetrahydrobiopterin
TPH	=	tryptophan hydroxylases
TNF-α	=	tumor necrosis factor alpha
T2DM	=	type 2 diabetes mellitus
TH	=	tyrosine hydroxylase

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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