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Review Article

Bioactive Peptides and Their Potential Use for the Prevention of Diseases Associated with Alzheimer's disease and Mental Health Disorders: Food for Thought?

Maria Hayes*

Department of Food Biosciences, Teagasc Food Research Centre, Ireland

***Corresponding author**

Maria Hayes, Food BioSciences Department, Teagasc Food Research Centre, Ashtown, Dublin 15, Ireland,Tel: 353 (0) 1 8059957; Email: maria.hayes@teagasc.ie

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Abstract

It has long been established that nutrients can affect cognition, mood and mental health. Nutrients can act on receptors in the peripheral nervous system or through direct inhibition of enzymes important in the regulation of mental health and other age related diseases including diabetes and multiple sclerosis. These enzymes include but are not limited to Acetyl cholinesterase (AChE), β-site APP cleaving enzyme(BACE1), Prolylendopeptidase (PEP) and Dipeptidyl peptidase 4 (DPP-IV). Bioactive peptides or cryptides are generated from food proteins by hydrolysis with proteolytic enzymes, fermentation with generally recognised as safe (GRAS) bacteria and through food processing. This paper collates current information on food derived peptides with the ability to inhibit enzymes important in the prevention of diseases associated with mental health disorders such as AD. It details potential peptide "hits" against enzyme targets currently examined and describes known, food-derived peptides that hold potential for future development as drugs and/or functional foods. It also discusses the blood brain barrier (BBB) and their potential transport across this barrier.

ABBREVIATIONS

AD:Alzheimer's Disease; ACE-I: Angiotensin Converting Enzyme-I; Ache: Acetylcholinesterase; APP: Amyloid Precursor Protein; Aβ: Beta-Amyloid; BBB: Blood Brain Barrier; BACE1;Beta-Site APP Cleavage Enzyme: Cecs: Cerebral Microvessel Endothelial Cells; CNS: Central Nervous System; DPP-IV: Dipeptidyl Peptidase 4; GLP-1:Glucagon Like Peptide 1, Hcmec/D3: Human Cerebral Microvascular Endothelial Cells :Insp: Inositol Phosphate; MS: Multiple Sclerosis; PEP: Prolylendopeptidase; POP: Prolyoligopeptidase; PTSD: Post Traumaticstress Disorder; T2D:Type 2 Diabetes; TDC: 2, 2', 4'-Trihydroxychalcone

INTRODUCTION

Since medieval times, food has been considered a tool to help modify temperament and mood and human nutrition and dietary influences are known to affect brain chemistry. Indeed, many neuroactive substances have been identified from foods previously [1] and food is known to affect our sleeping patterns, mood and overall mental health. For example, short and long-term forced dietary interventions can bring about changes in brain structure, plasticity, chemistry and physiology [2]. Amyloidosis is associated with the development of several diseases including Alzheimer's disease (AD), Multiple Sclerosis (MS), Parkinson's disease, adult onset diabetes, endocrine tumours and macular degradation [3]. Indeed, significant epidemiological evidence has emerged which suggests that mental health diseases including AD belong to the "diseases of civilisation" caused by modern western diets. Just as diet is implicated by many as a cause of mental health disorders several researchers have suggested that foods, and in particular, fermented foods have the potential to influence brain health due to a direct influence on the consumers microbiota which could enhance antioxidant and anti-inflammatory activities, reduce intestinal permeability and improve glycemic control, all of which have a positive influence on nutritional status, neurotransmission and neuropeptide production [4]. Several gut hormones that can enter the brain, or that are produced in the brain itself, influence cognitive ability. Regulators

of synaptic plasticity, such as brain-derived neurotrophic factor, can function as metabolic modulators, responding to peripheral signals such as food intake [5].It is therefore not surprising that food bioactive compounds including fatty acids [6] and peptides [7] are currently of interest for potential use in the prevention of mental health disorders such as AD. Indeed, bioactive peptides can be produced as a result of fermentation processes [8-11].

Bioactive peptides or cryptides are sequences of between 2-30 amino acids in length that can impart a health benefit to the consumer which goes above and beyond basic, human nutrition [12]. Cryptides can be released by enzymes during food processing, ripening and heating; during storage and by *in vitro* proteolysis [13,14] as well as by generally recognised as safe (GRAS) beneficial bacteria during fermentation [15]. Known peptide bioactivities include antihypertensive and angiotensin I converting enzyme (ACE-I) inhibitory actions [16], renin inhibition [17], dipeptidyl peptidase 4 (DPP-IV) inhibition [18], anti-inflammatory, opioid [19], satiety-inducing and anti-cholesterol activities as well as a myriad of others [16]. In addition to enzyme inhibition, opioid peptides play an active role in brain health as they are active in the nervous system and are pharmacologically similar to opium [19]. Opioid peptides are receptor ligands with agonistic or antagonistic activities and are characterised by distinct *N*-terminal sequences. Opioid peptides are similar to enkephalins as both have affinity for opiate receptor and display opiate-like effects which can be inhibited [19]. Examples include casomorphins, exorphins and rubiscolins [20]. The effect of these peptides varies, but they all resemble opiates. The opioid food-derived peptides are typically 4-8 amino acids in length.

Alzheimer's disease is the most common cause of dementia globally in aging societies. It is a neurodegenerative disorder characterised pathologically by plaque formation, where the major constituent is the amyloid beta peptide (Aβ), a 39-43 amino acid peptide derived from proteolytic processing of amyloid precursor protein (APP) [21,22]. Insoluble Aβ forms filaments and senile plaques in the brain [23]. The non-physiological metabolism of APP most frequently occurs due to damage of the cellular membrane bilayer and exposure of APP to scavenger lysosomes [20]. Phosphatidylcholine, a precursor of acetyl choline is affected and tau protein becomes heavily phosphorylated and glycated. It forms deposits in the white matter of the brain, causing nerve tangles which affect this communication network and this subsequently causes further neuron damage [24].The β-amyloid (Aβ) cascade and tau protein hyperphosphorylation are the theories that have been widely

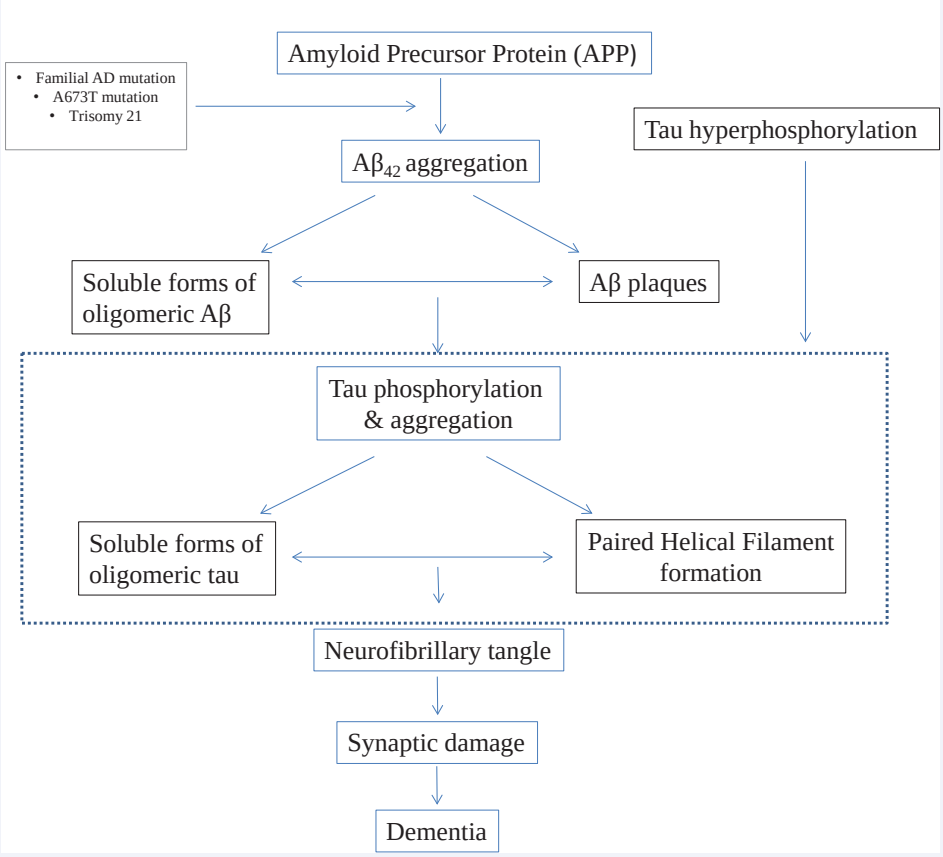

Figure 1 Amyloid cascade with the tau protein at the centre
Aβ42is formed from APP following mutations. The enzyme BACE1 plays a central role in the formation of Aβ42.Multiple phosphorylation events of tau play a crucial role during AD-related tau pathology. Tau is aprotein that regulates microtubule stability. During the development of AD, tau becomes abnormally phosphorylated or hyperphosphorylated, dissociates from microtubules and aggregates into neurofibrillary tangle which result in synaptic damage and eventually, dementia.

accepted for AD pathogenesis (Figure 1). Compounds that block the formation of Aβ may ultimately be clinically useful for treating AD [7,25].

The involvement of enzymes in the development of neurodegenerative disorders is well recognised [26,27]. Several enzymes including Acetylcholinesterase (AChE), (EC 3.1.1.7), Prolyl endopeptidase(PEP) or oligopeptidase (POP) (EC 3.4.21.26), and β-site APP cleaving enzyme, (BACE1) (EC 3.4.23.46) are thought to be suitable targets for drugs and food-derived peptides for potential prevention of tau protein hyperphosphorylation and the Aβ cascade [28]. Moreover, impaired glucose metabolism is closely linked to AD development and some researchers refer to AD as Type 3 diabetes. Furthermore, T2D has been identified as an additional risk factor for the development of AD [29]. Therefore, inhibition of enzymes such as DPP-IV that are thought important in the development of type 2 diabetes may have implications for the development of AD and other mental health disorders. Pharmacological agents, such as DPP-IV inhibitors, which increase the level of glucagon-like peptide-1 (GLP-1) and ameliorate T2D, have become valuable candidates as disease modifying agents in the treatment of AD.

Food components and diet are important for human health. The aim of this paper is to collate data concerning the enzymatic inhibitory role of food derived peptides and how this may prevent the development of mental health disorders that result due to amyloidosis.

Aβ formation

Several diseases that occur in the elderly are based on or associated with amyloid-like proteins and may be characterised by the build-up of extracellular deposits of amyloid or amyloid-like material that contribute to pathogenesis [30].In the development of AD, the first proteolytic step in the processing of amyloid precursor protein (APP) to amyloid-beta (Aβ) in the brain is performed by β-site APP cleaving enzyme [31]. BACE1is a membrane-bound, aspartic protease with high homology with the catalytic domain of renin and pepsin [32]. BACE1 is the β-secretase essential for Aβ plaque generation. It functions in the first step of the pathway leading to the production and deposition of Aβ. BACE1 is critical for Aβbiosynthesis and it is likely that factors that elevate BACE1 may lead to increased Aβ generation and promote AD as we get older [28,33].

BACE1 inhibition

Inhibition of BACE1 using natural products has provided promising results in AD therapeutics. Phenolic compounds such as catechins obtained from Green tea [34], lavandulyl flavanones extracted from *Sophora flavescens*[35], resveratrol obtained from red wine (*Vitis vinifera*), [36]and TDC obtained from *Glycyrrhiza glabra*[20] have all shown promising results in animals and *in vitro.* Recently, Cox and co-workers identified the flavonoids epicatechin and epigallocatechin as potent inhibitors (active in nanomolar quantities) of amyloidogenic APP processing using *invitro* screening of dietary flavonoids in primary neurons [37]. In addition, substrate-based, pentapeptidic β-secretase (BACE1) inhibitors with a hydroxyl methyl carbonyl isostere were also identified recently and showed potent BACE1 inhibitory activity in enzyme and cell assays, with one peptide, KMI-429, showing *in vivo* inhibition of Aβ production [38]. In addition, Lu identified the compound L655, 240 – a new type of BACE1 inhibitor which was found not to inhibit other aspartic proteases including renin and cathepsin D but which was specific in inhibiting BACE1 directly and which effectively decreased Aβ40, Aβ42 and APPβ production [39] More recently, Lazarus and colleagues [21] patented a group of polypeptide and peptide inhibitors of BACE1 that bind to the active site in a non-canonical fashion. However, due to the difficulty in developing drugs that can efficiently cross the blood-brain barrier (BBB) and reach appropriate therapeutic concentrations in the cerebral parenchyma without causing other side effects, few BACE1 inhibitors have been marketed to treat AD and those that have been developed are now in phase 1 of clinical trials [39].

PEP/POP enzyme

Prolyl oligopeptidase (POP) or Prolyl endopeptidase (PEP) (EC 3.4.21.26), is a proline-specific endopeptidase that is expressed in the brain and is known to cleave neuroactive peptides implicated in memory, learning and also in neurodegeneration [40]. It is highly conserved and cleaves peptide bonds at the carboxyl side of Proline residues in proteins with a relatively small molecular weight (30 amino acids in size) containing the recognition sequence X-Pro-Y, where X is a peptide or protected amino acid and Y is either an amide, a peptide, an amino acid, an aromatic amine or an alcohol [41,42]. Furthermore, it is thought that POP may be involved in thalamocortical neurotransmission, memory and learning functions of hippocampal formation and GABAergic regulation of voluntary movements. Tenorio-Laranga and colleague also identified the involvement of POP in the development of Multiple Sclerosis (MS). Welches and colleagues found thatPOP is also a major component of the enzymatic pathways that participate in angiotensin metabolism in canine hypothalamus [43]. Rossner and colleagues found that expression of POP in adult and aged transgenic mice which expressed Aβ plaques was increased in parallel with memory deficits prior to the appearance of Aβ plaques [44]. Furthermore, abnormal POP activity levels were reported previously in the brains of Alzheimer's patients [45]and increased POP activity is also observed in patients with bipolar disorder (manic), schizophrenic and post-traumatic stress disorder (PTSD) [42,46-48]. It is thought that POP functions in relation to mood disorders by acting as a regulator of inositol phosphate (InsP) signalling thereby modulating the effect of inositol depleting drugs such as Lithium in the treatment of bipolar disorder [49].

PEP/POP inhibition

Previously it was proposed that alterations in the level of POP activity in Alzheimer's disease and dementia account for some of the observed changes in neuropeptide levels. In Alzheimer's disease, vasopressin and substance P levels decrease in cortical areas and the hippocampus [50]. Manipulations of POP activity and its secondary effects on neuropeptide levels could represent a potential therapeutic target for treatment of cognitive disorders [50]. Several POP inhibitors have been isolated from microbes, medical plants and foods or have been chemically synthesised in recent times and their anti-amnesic effects have been studied in

rat models. Sørensen and colleagues found that peptide fractions generated from cod, salmon and trout hydrolysates, autolysates, and water-soluble extracts of cheeses inhibited POP [51]. Natural POP inhibitors have also been isolated from wine [52], casein [53]unsaturated fatty acids[54]and plant phenolics [55]. More recently, a protease treated sample of 'Barquillo' (Table 1) was found to inhibit POP *in vitro*. 'Barquillo' is a by-product obtained from cocoa processing by pressing and rolling cocoa butter. It is of high biological value due to its high protein content of between 20-27%. Furthermore, this hydrolysate was examined in the *Caenorhabditis elegans* Aβ model for oxidative stress and Aβ peptide toxicity. A tridecapeptide with the sequence DNYDNSAGKWWVT was identified as an inhibitor of Aβ plaque formation and β-Amyloid peptide toxicity. Morerecently, POP inhibitory polypeptides were identified from hydrolysates of Barbelfish skin gelatine [56].

Acetylcholinesterase (AChE)

Cholinergic abnormalities, alongside senile plaques, neurofibrillary tangles, and extensive neuronal loss, are the major characteristics in Alzheimer's disease (AD). AChE present in the Central Nervous System (CNS) catalyzes the hydrolysis of ACh to choline (Figure 2). ACh is released in the synaptic cleft, where it activates both postsynaptic and presynaptic cholinergic receptors, which results in cognition improvement. AChE – a cholinesterase enzyme - terminates this neural-stimulating activity [57]. In AD sufferers, a deficit of this neurotransmitter is observed – the so-called cholinergic hypothesis.AChE (EC3.1.1.7) is implicated in the pathogenesis of Alzheimer's disease. AChE is thought to directly interact with Aβ in a manner that increases the deposition of this peptide into insoluble plaques [58]. This suggests that AChE inhibitors might be able to act as disease-modifying agents rather than as mere palliatives [58].

AChE inhibitors

AChE inhibitors are used in the treatment of AD. Drugs used at the present time as AChE inhibitors include tacrine, rivastigmine and donezepil. However, these possess some side effects including nausea, vomiting and diarrhoea [59]. Plants are rich sources of pharmaceuticals and a study of Brazilian plants showed excellent results for AChE inhibition with the species *Amburana cearensis, Lippia sidoides, Paullinia cupana, Plathymiscium floribundum* and *Solanum asperum* [60]. These plants were used in traditional medicine for the treatment of memory dysfunction for centuries [61]. Coumarin is a vanilla like phytochemical found in cassia cinnamon. Previously, a set of 19 coumarin and 2 chromone derivatives with known inhibitory activity toward monoamine oxidase (MAO) A and B were tested as acetylcholinesterase (AChE) inhibitors. All compounds inhibited AChE with values in the micromolar range (3–100 μM). A kinetic study showed that most compounds acted as noncompetitive AChE inhibitors. More recently, polysaccharide–peptide complexes were identified in *Cordyceps militaris* (CPSPs) and characterized for their AChE inhibitory properties. Three polymers (CPSP-F1, -F2, and -F3) were extracted and separated by ultrasound-assisted extraction and diethylaminoethanol (DEAE)–Sepharose CL-6B column chromatography. CPSP-F1 and CPSP-F2 exhibited half maximal inhibitory concentrations of 32.2 ± 0.2 mg/mL and 5.3 ± 0.0 mg/mL [62]. A number of phytochemical extracts have also demonstrated AChE inhibitory activities. For example, phytochemical studies on the ethanolic extract of *Barleria prionitis*, a plantof Sri Lankan origin, resulted in the isolation of a new compound, balarenone (1), along with three known compounds, pipataline (2), lupeol (3) and 13, 14-seco-stigmasta-5, 14-diene-3-α-ol (4). These compounds showed moderate inhibitory activity against glutathione S-transferase(GST) and AChE [63].

Protein hydrolysates are also a source of AChE inhibitory peptides (Table 1). Tuna liver is a fish by-product and is normally discarded and/or used as fish and animal feed due to poor functionality. In a study carried out by Ahn and colleagues, tuna fractionated hydrolysates produced by the commercial enzymes Alcalase, Neutrase and Protamex following Flavourzyme hydrolysis showed excellent antioxidant activities against DPPH. Furthermore, all fractionated hydrolysates inhibited acetylcholinesterase activity and the high MW fractions showed greater AChE inhibitory activities than LMW fractions [64]. The AChE inhibitory activity of Douchi – a traditional Chinese salt-fermented soybean food was examined and observed inhibition was attributed to bioactive peptides generated from soybean protein following fermentation [65]. Similarly, the AChE inhibitory activity of Chinese sufu (fermented tofu) was observed by Chen and colleagues [66]. In a further study which examined the anti-obesity and anti-Alzheimer's effect of rice bran, bioactive peptides <5kDa in size were identified [67].

DPP-IV

It is estimated that the incidence of diabetes globally will increase from 285 to 439 million by 2030 [68]. Blood vessel damage in the brain of patients with diabetes and high cholesterol can lead to symptoms of Alzheimer's disease and prevention of diabetes and high cholesterol can help to reduce the risk of developing AD [69]. Type 2 diabetes (T2D) is characterised by abnormally high blood glucose levels due to insulin resistance. Chronic T2D also negatively affects the CNS and constitutes a known risk factor for dementia. Recently, researchers have suggested that AD might be a neuroendocrine-like disorder and have termed it "Type 3 diabetes" or "brain-specific diabetes" [70,71]. Insulin is a common bridge between T2D and AD as insulin signalling is involved in the regulation of Aβ plaque and neurofibrillary tangle formation, the two major neuropathological hallmarks of AD [68].During chronic T2D and chronic glucose dysmetabolism brain damaging effects may arise and advanced glycation end products (AGEs) are formed[72]. The extent of Aβ peptide glycation by AGEs is correlated with its aggregation into senile plaques as well as with tau protein hyperphosphorlyation and the formation of neurofibrillary tangles [73]. There is therefore promising potential in the use of anti-diabetic drugs and peptides in the prevention and treatment of AD.

DPP-IV inhibitory peptides

Diets rich in specific biofunctional ingredients, including food protein derived peptides, have emerged as a potential strategy for the prevention and management of T2D [74, 75]. Dipeptidyl peptidase-4 is a highly specialized, membrane boundaminopeptidase that demonstrates wide tissue distribution and is present in soluble form in the plasma. Glucagon-like peptide

Table 1:

Food source	Bioactive compound	Inhibitory activity	Reference
Green tea	Catechins	BACE1	Jeon et al., 2009
	Epicatechins	BACE1	Cox et al., 2014
Red wine	Resveratrol	BACE1	Choi et al., 2009
Sopherea flavescens	flavanones	BACE1	Jwang et a., 2008
Cod hydrolysate	peptides	POP inhibition	Sorensen et al., 2004
Trout hydrolysate	peptides	POP inhibition	Sorensen et al., 2004
Salmon hydrolysate	peptides	POP inhibition	Sorensen et al., 2004
Cheese	peptides	POP inhibition	Sorensen et al., 2004
Red wine	unknown	POP inhibition	Yanai et al., 2003
Casein	peptides	POP inhibition	Asano et al., 1991
Cocoa 'Barquillo'	tridecapeptide	POP inhibition	Martorell et al., 2013
Barbel fish skin gelatine	peptides	POP inhibition	Sila et al., 2015
Cassia cinnamon	coumarin	AChE inhibition	Razavi et al., 2013
Barleria prionitis	balarenone	AChE inhibition	Tsai et al., 2014
Barleria prionitis	pipataline	AChE inhibition	Tsai et al., 2014
Barleria prionitis	lupeol	AChE inhibition	Tsai et al., 2014
Tuna	bioactive peptides	AChE inhibition	Ahn et al., 2010
Salt fermented soybean food -Douchi	bioactive peptides	AChE inhibition	Liu et al., 2009
Fermented tofu - Chinese Sufu	bioactive peptides	AChE inhibition	Chen et al., 2012
Rice bran	bioactive peptides <5kDa	AChE inhibition	Kannan et al., 2012
Dairy hydrolysate	bioactive peptides	DPP-IV inhibition	Harnedy et al., 2015
Salmon hydrolysate	bioactive peptides	DPP-IV inhibition	Harnedy et al., 2015
Tuna hydrolysate	bioactive peptides	DPP-IV inhibition	Harnedy et al., 2015
Amaranth	bioactive peptides	DPP-IV inhibition	Harnedy et al., 2015
Red seaweed *Palmaria palmata*	peptides	DPP-IV inhibition	Harnedy et al., 2015
Bran rice hydrolysate	tridecapeptide	DPP-IV inhibition	Kannan et al., 2012
Wheat gluten	exorphins	opioid inducing	Zioudrou et al., 1979
α-casein	beta-casomorphine-7	opioid inducing	Zioudrou et al., 1979
ovine first milk - clostrum	Proline-rich polypeptide complex	opioid inducing	Leszek et al., 1999
Fermented milk - *Lactobacillus helveticus*	bioactive peptides	opioid/AChE/BACE1 inhibition	Yeon et al., 2010

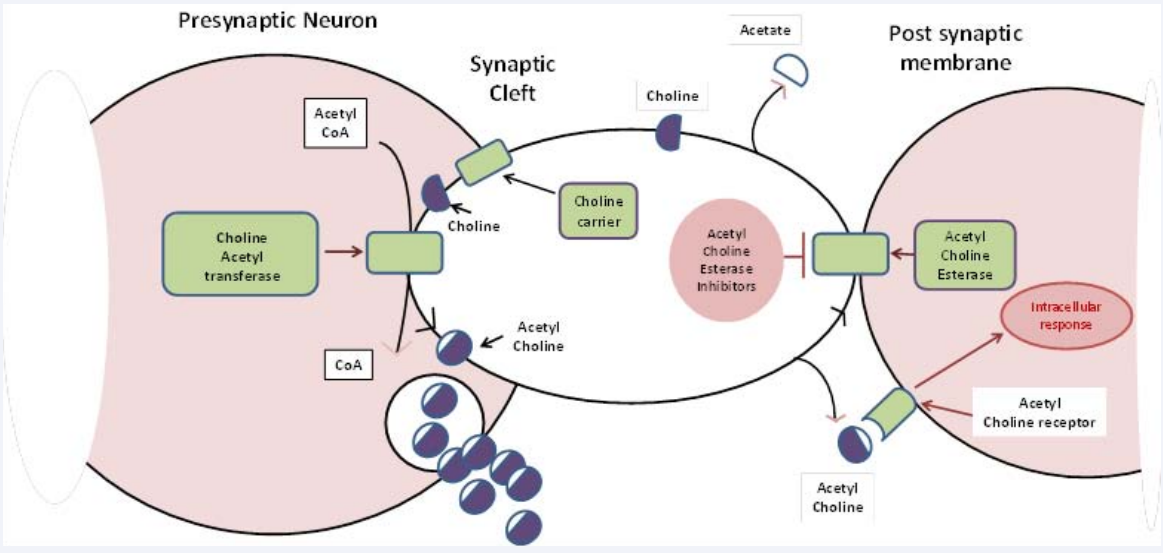

Figure 2 Acetylcholinesterase inhibitor during cholinergic nerve transmission.
Acetylcholine is produced in the presynaptic neuron by the enzyme choline acetyltransferase from acetyl-coenzyme A and choline. It is released in the synaptic cleft where it binds to the acetylcholine receptor. This triggers an intracellular response and synaptic transmission is terminated by acetylcholinesterase which hydrolyses acetylcholine into acetate and choline. Choline is transported into the presynaptic neuron by the choline carrier and serves as a substrate for the described production of acetylcholine. Acetylcholinesterase prevents the breakdown of acetylcholine into acetate and choline and prolongs acetylcholine duration

1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP) both control blood glucose levels in the body [76]. These are degraded by DPP-IV and several research groups are looking at the development of DPP-IV inhibitory agents to control glucose and prevent T2D [77]. Pharmaceutical DPP-IV inhibitory drugs available today include Saxagliptin (Onglyza ™), and vildagliptin (Galvus ®). These drugs do have some side effects including urinary and upper tract infections [78]. Food derived bioactive peptides that inhibit DPP-IV provide an alternative for the potential prevention and treatment of both T2D and AD. Recently, Amylin, a pancreatic peptide, 37 amino acids in length which passes through the BBB easily provided the template for the amylin analog pramlintide which serves as an effective drug in the clinical treatment of T2D [79]. Furthermore, when injected, this peptide reduced behavioural impairment and brain amyloid pathology in murine models of Alzheimer's disease [79].

Peptides derived from dairy, salmon, tuna, rice, amaranth and lysozyme proteins were found previously to inhibit DPP-IV *in vitro.* Furthermore, thirteen peptides were identified from a Corolase PP hydrolysate of the red macroalga *Palmaria palmata* (Harnedy et al., 2014). Kannan identified a pentapeptide from a bran rice hydrolysate which showed enhanced anti-Alzheimer's activity. Few *in vivo* studies with DPP-IV inhibitors have been carried out to date in relation to their possible role in the prevention of AD. Several recent reports however have identified that dipeptidyl DPP-IV inhibitors have suppressive effects on atherosclerosis in apolipoprotein E-null (*Apoe*$^{-/-}$) mice [80]. Furthermore, the protective effects of the DPP-IV inhibitor sitagliptin in the blood-retinal barrier in a T2D animal model were shown previously [81].

The psycho-immuno-enhancing activity of peptides

The opioid system may be involved in the development of AD, including in; cognitive impairment, hyper phosphorylated tau formation, Aβ production, and neuro inflammation [82]. Opioid receptors can influence neurotransmitters involved in the development and pathogenesis of AD including acetylcholine, norepinephrine, GABA, glutamate, and serotonin. Non-function of opioid receptors can retard degradation of BACE1 and γ-secretase and is known to up-regulate BACE1 and γ-secretase and the production of $A\beta_{42}$ (Cai & Ratka, 2012)[82]. Therefore, the opioid system is a suitable target for peptides and drugs to potentially delay and prevent the development of AD.

Dietary protein including wheat gluten and α-casein are rich sources of bioactive and opioid peptides (Table 1) including exorphins (wheat gluten derived) and beta-casomorphine-7 from β-casein.[83,84].Colostrinin® is a proline-rich polypeptide complex isolated from ovine colostrum that previously demonstrated immunomodulatory properties in mice, rats and chickens and was identified as a cytokine-like factor that acts as an inducer of interferon γ and other cytokines in the human peripheral blood and cord blood leukocyte cultures. Colostrinin® also demonstrated psycho-immuno enhancing activity in volunteers and was studied for its effect on patients with AD. It was found that administration of Colostrinin® to patients with mild to moderate dementia improved their condition. Studies in rats, demonstrated that the memory of rats increased and the speed of memorization of new information was accelerated [85]. The opioid effect of food-derived bioactive peptides is well documented and the role of casomorphins in the CNS is well recognised. Recently [86] an ethanol precipitate from fermented milk with *L. helveticus* IDCC3801 was found to improve APP metabolism and memory deficit in rats. Using acell-based assay and wild type APP and β-secretase over-expressing cells, the ethanol precipitates of the fermented milk cultured with *Lactobacillus helveticus* IDCC 3801 were found to induce a strong decrease of APP β level in amyloidogenic pathway toward β-amyloid production of APP processing. When administered orally to rats, the ethanol precipitate significantly reduced Aβ level in serum. In the scopolamine-treated mouse model, the ethanol precipitate also attenuated memory deficit [86].

Transport of peptides across the blood brain barrier (BBB) and suitable *in vitro* models

The blood-brain-barrier is the active interface between the circulatory system and the central nervous system (CNS). It functions to restrict the transport of toxic substances to the brain and it acts as a carrier for the transport of nutrients to the brain and removal of metabolites [87]. It is a significant hurdle in the treatment of CNS disorders such as AD. The delivery of peptide drugs and food-derived peptides to the brain is limited to small, predominantly hydrophobic molecules and is through receptor mediated transcytosis (RMT) [88]. Transcytosis in the BBB endothelial cells is poorly understood. Several *in vitro* transcytosis assays have been developed but these often represent paracellular flux rather than transcytosis in endothelial cells. Recently however, an *in vitro* model of the human BBB using immortalised human cerebral microvascular endothelial cells (hCMEC/D3) to quantitatively measure protein/peptide transcytosis was developed and validated [88]. For bioactives with MW greater than 4000 Da, the permeability profile is similar to that of bovine and porcine cerebral microvessel endothelial cells (CECs) [89]. This model has been used widely to study the toxic effects of Aβ peptides on brain microvasculature in AD. This model could be useful for assessing if food-derived DPP-IV, POP, AChE inhibitory peptides and AD preventative drugs can reach their targets in the brain.

CONCLUSION

T2D patients can often develop dementia and T2D patients' also often present hyperglycemia and insulin signalling dysfunction. Moreover, anti-T2D drugs are now in trials for dementia therapy and some were shown as beneficial against Aβ plaque formation. Food derived peptides that inhibit enzymes important in the development of Aβ plaque and tau protein hyper phosphorylation offer potential therapy for the prevention and alleviation of mental health disorders such as AD and warrant further research. However, transfer of knowledge from *in vitro* and animal bioassay to humans is an important consideration and models to predict transcytosis should also be researched further.

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