

# Bioactive Peptides in Neurodegenerative Diseases

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## **1. Introduction:**

Bioactive peptides, isolated small fragments of proteins, are involved in several biological activities and significantly contribute to human physiological responses. Recent years have witnessed an increasing number of researches focus on the application of these peptides as therapeutic agents in disease management. A wide range of therapeutic effects including antimicrobial, anti-cancer, antidiabetic, antioxidant and inhibition of neurodegenerative diseases (NDDs) have been proposed for bioactive peptides effects (Baig et al., 2018).

The existing agents for prevention or treatment of NDDs are insufficient, and the number of drugs approved is limited by the high failure rates in clinical trials (Morris et al., 2014). Several lines of evidence indicate that peptides are pivotal tools for NDDs research including basic and clinical studies and can be used to study the properties of misfolded proteins and/or peptides.

This chapter offers a brief introduction to bioactive peptides application in neurodegenerative diseases. We discuss the successful application of synthetic peptides and their natural counterparts in drug discovery along with their drawbacks and limitation. In addition, we discuss the therapeutic utilities and versatilities of peptide inhibitors in various neurodegenerative disorders as therapeutic drug candidates.

## **2. Neurodegenerative diseases: definition and classification**

Neurodegenerative diseases (NDDs) are progressive degenerative conditions characterized by loss of neurons within the brain associated with proteins deposition and changes in neurochemical properties in the central nervous system and peripheral

organs (Kovacs, 2019). Considering the increase in the elderly population in recent years, age-dependent disorders such as NDDs are becoming increasingly prevalent (Heemels, 2016). Major neurodegenerative diseases include Parkinson's disease (PD), Alzheimer's disease(AD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia and the spinocerebellar ataxias. These diseases are diverse in their clinical manifestations; some affecting person's movement ability and others affecting memory and cognitive impairments, speak and even breath (Gitler et al., 2017).However, they share some common neuropathological mechanisms. A comprehensive understanding of the causes and mechanisms of these diseases, is crucial for enabling scientists to develop suitable treatments.

Misfolded proteins, aggregation and accumulation of proteins are the main pathological events in neurodegenerative disease therefore uncovering the role of the unfolded protein response seems to be one important strategy in treatment of these diseases (Cornejo & Hetz, 2013). Furthermore, changes in protein elimination mechanisms, such as the ubiquitin-proteasome system and the autophagy-lysosome pathway, have high impact on the pathogenesis (A.T. Nijholt et al., 2011).

Several molecular pathways contribute to the chronic damage of neurons, for instance, chronic excitotoxicity induced by glutamate has been reported for progressive neurodegeneration in AD, ALS, and HD(Lewerenz & Maher, 2015). Other important pathways are energetic dysregulation, metabolic changes, dysregulation of ion homeostasis, and adaptation that have been shown to play role in neurodegenerative disorders (Von Bernhardi & Eugenín, 2012).

The role of misfolded proteins and their deposition in neurodegenerative disease have been established over past decades (Table 1).

### **Table. 1**

#### **2.1 Alzheimer disease:**

Dementia is identified as acquired loss of cognition in multiple cognitive domains severe enough to interfere with social or occupational activities of daily living. It has been reported that two-thirds of cases of dementia in people age 65 and older are caused by Alzheimer's disease (AD). Onset of disease before 65 years old is unusual and seen in less than 10% of Alzheimer's disease patients. This type of neurodegenerative disease progressively impairs the behavioral and cognitive functions such as memory, attention, comprehension, judgment and etc. (Arvanitakis et al., 2019).

The early presenting sign is episodic short-term memory loss and relative sparing of long-term memory. In the early stages of disease, impairment in executive activity ranges from subtle to significant. Then language disorder and impairment of visuospatial skills might be represented. Also, neuropsychiatric symptoms such as agitation, apathy, psychosis disinhibition and social withdrawal are also common in the mid to late stages. In the late stages of disease, motor tasks and olfactory dysfunction, parkinsonian, dystonia and akathisia, and also sleep disturbances symptoms occur (Kumar et al., 2021).

There are macroscopic and microscopic features for Alzheimer's disease. In fact, there is no single feature or combination of features as a specific marker, but there are some features are highly suggestive in diagnosis of AD. It has been documented that a

moderate cortical atrophy is present in the brain of patients. The frontal and temporal cortices show an enlarged sulcal spaces with atrophy of the gyri, whereas the primary motor and somatosensory cortices appear unaffected (Perl, 2010). A growing atrophy in posterior cortical areas has also been observed in AD brain, most notable the precuneus and posterior cingulate gyrus, driven partly by functional imaging studies (Rami et al., 2012).

There are some other microscopic features like amyloid plaques, Neuritic plaques and neurofibrillary tangles (NFTs). Senile amyloid plaques are formed through the extracellular nonvascular accumulation of A $\beta$ 42 and A $\beta$ 40 peptides as a result of imbalance in the production and clearance pathways and abnormal processing of APP (amyloid precursor protein) by the  $\beta$ - and  $\gamma$ -secretases (DeTure & Dickson, 2019). These small peptides (4 kDa) fold into highly fibrillogenic beta-pleated sheet structure. Cored neuritic plaques are another microscopic feature containing tau protein (Tau-positive neurites) usually have a central zone of dense amyloid, sometimes forming a compact core (Dickson, 1997), while some neuritic plaques contain activated microglia and reactive astrocytes. In addition, some of the dystrophic neurites associated with neuritic plaques contain tau filaments, which can have a paired helical filament morphology are liable to be observed with electron microscopy (Serrano-Pozo et al., 2011).

Formation of NFTs is another hallmark of AD. It was first described as “neurofibrils,” which forms thick bundles near the surface of affected neurons (Ryan et al., 2015). Amyloid plaques, especially cored neuritic plaques, and NFTs contain of filamentous tau proteins are required for neuropathologic diagnosis of AD (DeTure & Dickson, 2019).

Like other neurodegenerative disease, so far, there is no specific cure for Alzheimer's disease, although there are some available drugs that may improve the symptoms. Only very recently we can state that FDA has approved, after almost 30 years, a novel and very promising drug against AD which is a monoclonal antibody, called Aducanumab, able to contrast the b-amyloid fibrils and inducing a significant reduction of amyloid plaques (<https://doi.org/10.1002/alz.047259>). This is the first approved drug directly contrast amyloid plaques formation. Aducanumab seems to provide clinically meaningful benefit in association with amyloid lowering (PMID: 33971962), from now on the clinical phase 4 starts and we will wait for observation in larger cohorts.

Classically AD is clinically treated with cholinergic agents which improve and maintain cognitive abilities in patients with mild-to-moderate AD. Also, some neuroprotective supplements are used as complementary medicine. Therefore, novel treatments that preserve cognitive ability and prevent the progression of AD are needed.

## **2.2 Parkinson's disease:**

As the second most common neurodegenerative disease, Parkinson's disease is characterized by a progressive loss of dopaminergic neurons in the substantia nigra pars compacta. Rest tremor, rigidity, bradykinesia and postural instability, and a variety of other motor and non-motor symptoms including anxiety and depression are known as clinical symptoms in PD (Obeso et al., 2017). Both genes and environmental/lifestyle factors contribute to the pathogenesis of PD. Age is known as the most important risk factor, since the disease onset is mostly around 60 years (Simon et al., 2020), therefore, age dependent biological failures like telomere dysfunction, epigenetic

changes, mitochondrial defects, ubiquitin-proteasome system (UPS) and autophagy-lysosomal system play role in pathophysiology of Parkinson's disease (González-Casacuberta et al., 2019; Pohl & Dikic, 2019).

It is now well established that PD is a systemic disorder and alpha-synuclein is a key player in disease progression. Alpha-synuclein, a neuronal protein of 140 amino acids long was first isolated and sequenced in 1988. It is mainly located in presynaptic compartment, but it has been identified also in the nucleus, therefore, accounting for the name "synuclein" (SYNapse + NUCLEus, synuclein) (Maroteaux et al., 1988). The exact physiological activity of alpha-synuclein is still unclear but its connection to the pool of synaptic vesicles and synaptic transmissions suggest an its important role in the neurotransmitter release process, synaptic function and plasticity (Lashuel et al., 2013). Accumulation of aggregated alpha-synuclein within neurons results in the reduction of synaptic proteins, progressive decrease in neuronal excitability, and, finally, cell death (Volpicelli-Daley et al., 2011).

The treatment strategy for Parkinson's patients is mainly symptomatic, focused to improve their motor function such as tremor, rigidity, bradykinesia and non-motor symptoms like constipation, cognition, mood and sleep disorder. So far, no drug treatment capable of modifying the disease are present on the market. To ameliorate the motor symptoms, dopamine-based therapies are used. While non-motor symptoms require other approaches like cholinesterase inhibitors for cognition or use of selective serotonin reuptake inhibitors for psychiatric symptoms (Armstrong & Okun, 2020).

Studies to treat the non-motor symptoms of PD have shown that rivastigmine, donepezil, galantamine, and memantine, which are known as cholinesterase inhibitors

and N-methyl D-aspartate receptor antagonists, can improve the cognitive functions (Feldman et al., 2001; Szeto & Lewis, 2016). However, additional pharmacological studies should be carried out before these drugs are considered safe and tolerable, because there are potential adverse effects such as diarrhea, headache, and dizziness (Feldman et al., 2001; Szeto & Lewis, 2016).

### **2.3 Huntington's disease**

As the most common inherited neurodegenerative disease, Huntington's disease (HD) is identified by uncontrolled excessive motor movements and cognitive and emotional deficits (Paulson & Albin, 2011; Roos, 2010). HD is a dominantly inherited, neuropsychiatric disorder which affects generations of afflicted families. It always, starts in adulthood and progresses slowly over years with common and typical symptoms. The discovery of the HD mutation has also shed light on the possible mechanisms involved in disease. The significant variability in clinical symptoms and the different range in age of onset, even among affected members in the same family, are now recognized to stem directly from the type of mutation in HD (a dynamic repeat in a polyglutamine-encoding CAG tract) (Paulson & Albin, 2011). Onset of the disease is defined by the presence of a motor disorder, usually the involuntary movements known as chorea. In some patients, other motor abnormalities may lead to a diagnosis of HD (Louis et al., 2000). In some patients symptoms begin even before the age of 20 years with early behavioral disorders and learning problems at school (Juvenile Huntington's disease; JHD) (Roos, 2010).

Clinical symptoms of this “neuropsychiatric” disorder, including progressive movement disorder, progressive cognitive disturbance culminating in dementia; and various

behavioral disturbances that often precede diagnosis and can vary depending on the state of disease (Paulson & Albin, 2011).

HD is characterized by the overexpression of a misfolded protein called huntingtin derived from CAG codon repeat expansion in its own gene. CAG encodes the amino acid glutamine, so the expansion results in an abnormally long glutamine tract within the N-terminus of the huntingtin protein (Htt). The abnormal Htt results to be insoluble and can accumulate causing cell death. HD is part of a large family of other pathology collectively termed as “polyglutamine” diseases because they are caused by the overexpression of repeated CAG sequences (Zheng Z, Diamond MI. Huntington disease and the huntingtin protein. *Prog Mol Biol Transl Sci.* 2012;107:189-214. doi: 10.1016/B978-0-12-385883-2.00010-2.). Although Huntingtin is expressed in many tissues, the clinical symptoms of HD reflect CNS disorder, and histopathologic abnormalities are almost limited to the brain. However, there are investigations to evaluate the effects of expanded huntingtin in other organs (Borovecki et al., 2005; Chiang et al., 2007).

Like other neurodegenerative disease there is not a cure for Huntington's. There are some potential compounds or strategies considered for prevention or symptomatic treatments including neuroprotective and antiapoptotic compounds (Wei et al., 2001), transglutaminase inhibitors (Dubinsky & Gray, 2006), histone deacetylase inhibitors (Gardian et al., 2005), antioxidants, mitochondrial enhancers and etc.

#### **2.4 Amyotrophic lateral sclerosis**

Amyotrophic lateral sclerosis (ALS), a fatal motor neuron disorder, is characterized by progressive loss of the upper and lower motor neurons (UMNs and LMNs) at the spinal

or bulbar level (Rowland & Shneider, 2001). Finding the molecular mechanisms of neurodegeneration in ALS will help us to understand the disease's progress. Moreover, clarification of molecular mechanisms yields insight into discovering newer therapeutic approaches.

Mutation of the gene encoding the superoxide dismutase 1 (SOD1), antioxidant enzyme, has been reported as one of the most common cause of ALS (De vos et al., 2007; Ivanova et al., 2014). Misfolding in the mutated SOD1 enzyme can lead to aggregation in the motor neurons within the central nervous system (Forsberg et al., 2011). There are also other genes which are known to cause familial ALS including TARDBP (encodes TAR DNA-binding protein 43 (TDP-43)); FUS (encodes for fusion in sarcoma), ANG (codes for angiogenin, ribonuclease, and the RNAase A family 5), OPTN (codes for optineurin) and C9orf72 (Chiò et al., 2011; Corrado et al., 2010; Gijssels et al., 2012; Kabashi et al., 2011; Majounie et al., 2012).

There are four main types of ALS phenotypical expressions (Kiernan et al., 2011; Vucic & Kiernan, 2007; Wijesekera & Leigh, 2009) including

- 1- Limb-onset ALS: both upper motor neuron (UMN) and lower motor neuron (LMN) signs in the limbs are exist,
- 2- bulbar onset ALS: speech and swallowing difficulties followed by limb weakening in later stages of the disease ,
- 3- Primary lateral sclerosis (PLS) with pure UMN involvement,
- 4- progressive muscular atrophy (PMA) with pure LMN involvement.

As this classification illustrates the main clinical feature in the ALS is based on a combination of UMN and LMN damage. It has been demonstrated that almost 70% of

the cases among patients are affected with the limb-onset ALS. Bulbar onset accounts for 25% of the cases, and 5% of the cases having initial trunk or respiratory involvement (Kiernan et al., 2011). During the ALS progression, a distinctive feature of a combination of upper motor and LMN degeneration signs within the same CNS region appears in patients (Gordon et al., 2006) and eventually the main cause of death in patients is respiratory failure as the result of pulmonary complications (Corcia et al., 2008).

ALS such as Parkinson's disease is suggested to be due to both environmental and genetic factors and clinical trials have been conducted giving the same treatment to patients with ALS or PD (Lomen-Hoerth et al., 2002; Wijesekera & Leigh, 2009).

Recent three decades have witnessed the research on ALS to improve our understanding of the pathophysiology of disease. However, the translation of this efforts into effective treatments has been disappointing so far, and most cases with ALS didn't have the chance to participate in clinical trials (Kiernan et al., 2021). Although numerous novel potential treatments are being tested in Phase 1 to Phase 3 clinical trials ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)), no effective treatment currently exists able to stop the progression of ALS. The only disease-modifying treatment approved for clinical use by FDA, Riluzole, demonstrated to extend the life span in ALS patients (Miller et al., 1999). In primary investigations, 38,6% reduction in mortality was reported (Bensimon et al., 1994), and it has been associated with 35% improvement in survival with the 100 mg dose (Lacomblez et al., 1996).

### **3. Bioactive peptides**

Bioactive peptides are identified as chains of amino acid residues, derived from hydrolyzed food protein present in nature. These peptides can be extracted from

different food-derived animal, plants, and marine protein sources. They are health-protective molecules that, similar to hormones, can control many important body functions (Korhonen & Pihlanto, 2006; Lee & Hur, 2019; Udenigwe & Aluko, 2012). They are characterized by many properties with, for example, antioxidant, antihypertensive, anti-inflammation, anti-tumor, antimicrobial and neuroprotective effects (Assadollahi et al., 2019; Blondelle & Lohner, 2000; Kodera & Nio, 2006; Kudo et al., 2009; Lee & Hur, 2019; Majumder et al., 2016; McCann et al., 2014).

### **3.1 Bioactive peptides in neurodegenerative disease**

Like other biogenic compounds, the potency and efficacy of these peptides is completely depending on the structure and amino acid composition. In this section we provide a review on understanding the role of bioactive peptides and their applications in management of neurodegenerative diseases. To do this aim effect of bioactive peptides are described based on their mechanism of action.

#### **3.1.1 Role of bioactive peptides in regulation of reactive oxygen species (ROS) levels**

Reactive oxygen species (ROS) are highly reactive chemical molecules formed by the partial reduction of oxygen. Examples of these compound include superoxide anion ( $O_2^-$ ), hydroxyl radical ( $\cdot OH$ ), and hydrogen peroxide ( $H_2O_2$ ) (Ray et al., 2012).

Reactive oxygen species (ROS) and free radicals can attack and interact with the membrane lipids, protein and DNA in the cell. They can be of endogenous or exogenous origin, but in both cases oxidation by free radicals in the body have influence

on human health and may cause several chronic diseases like cancer, cardiovascular diseases, diabetes, and neurodegenerative disorders (Dong et al., 2008).

On the other hand, we know that the body is supported by several defensive antioxidant systems that can scavenge and transform ROS into harmless species (Yeung et al., 2002). The antioxidant enzymatic system includes catalase glutathione peroxidase (GSH-Px) (CAT), superoxide dismutase (SOD), and glutathione reductase (GR). There are also non-enzymatic antioxidants which are able to scavenge and eradicate the oxidative stress (McCord, 1993). Keeping the balance between ROS and body antioxidant is critical for avoiding oxidative stress and prevention of disease (Ghazizadeh et al., 2020).

The antioxidant activity of peptides isolated from natural compounds and food sources was reported by Marcuse in 1960 for the first time (Gomez-Guillen et al., 2011). Later several studies were done to confirm the antioxidant properties of these compounds extracted from plant and animal sources (Baltic et al., 2014). Despite numerous researches in this area, the exact antioxidant mechanism of these peptides still has not been completely understood. Compared with natural proteins, small peptides display more antioxidant activity and could be absorbed in the gastrointestinal system without further digestion (M. Liu et al., 2016).

Basically, antioxidant peptides can be classified into two main categories; endogenous and exogenous. Endogenous peptides produced naturally inside the cells such as glutathione, carnosine, anserine, GHL, whereas the exogenous type are derived from food proteins sources during gastrointestinal digestion (Gallego et al., 2020; J. Zhang et al., 2020).

It is believed that anti-oxidant peptides are free radical scavengers and they are able to prevent lipid peroxidation and chelate transition metal ions (Jiménez-Colmenero et al., 2010; Rajapakse et al., 2005; Suetsuna et al., 2000).

Oxidative stress, as the main cause of ROS generation, has an impact on neuronal cell death. There are some hydrolysates/peptides isolated from animal and egg proteins which are able to provide neuroprotection through inhibiting oxidative stress factors (Gu et al., 2018; Q. X. Zhang et al., 2015). It has been reported that a peptide (Met-Glu-Ile-Phe-Val-Lys-Thr-Lys-ThrGly) could protect PC-12 cells through prevention of nitric oxide and ROS generation and lipid peroxidation. Also, whey protein hydrolysates prevented DNA fragmentation by ROS. Stimulation of cellular antioxidant enzymes like superoxide dismutase (SOD) and catalase was reported as the main mechanism of action. Moreover, a small peptide, Pro-Ala-Tyr-Ser-Cys (PAYSC), obtained from anchovy hydrolysate inhibited ROS and malondialdehyde (MDA) production (Lee & Hur, 2019; Zhao et al., 2017). There are other reports indicating that hydrolysates isolated from plants showed significantly antioxidant activities by inhibiting ROS production and enhanced catalase and SOD enzymes activities in H<sub>2</sub>O<sub>2</sub>-treated neuronal cells (Chen et al., 2015; Zhu et al., 2013).

Several factors like method of proteins isolation, peptide concentration, degree of hydrolysis and type of protease used in the process, affect the antioxidant properties of peptides (Erdmann et al., 2008; Q. Liu et al., 2010). Other properties such as type and number of amino acids, as well as the order of amino acid sequence play a key role in their antioxidant activity (Erdmann et al., 2008; Rajapakse et al., 2005).

It has been reported that Tyr, Trp, Met, Lys, Cys, and His are the amino acids that contribute to antioxidant activity (Baltic et al., 2014). For instance, imidazole group of Histidine amino acid has been found to be in relation with the hydrogen donating, lipid peroxy radical trapping and the metal chelating properties, or cysteine SH group has been reported the main role in interaction with free radicals (Baltic et al., 2014; Sarmadi & Ismail, 2010). Recently it has been demonstrated that the presence of hydrophobic amino acids, such as proline, tryptophan, valine and phenylalanine in the small peptides (2–20 amino acids), provide a potent antioxidant activity (Ketnawa et al., 2018; Tadesse & Emire, 2020; Yang et al., 2019). While histidine-containing di-peptides, carnosine ( $\beta$ -alanyl-L-histidine) and anserine (N- $\beta$ -alanyl-1-methyl-L-histidine) are the most studied hydrophilic antioxidants exist in meat and in some fish. Carnosine and anserine protected the DNA, against L-3, 4-dihydroxyphenylalanine Fe (III) induced damage. Also, oral administration of L-carnosine was able to increase the total antioxidant capacity of human serum (Di Bernardini et al., 2011).

In addition, the configuration of amino acids has been showed to play role for example, substitution of L-His by D-His in a peptide results in diminish antioxidative activity (Baltic et al., 2014).

Type of meat, as the source of peptide, has been considered as a main factor in antioxidant activity, for example the concentration of carnosine in chicken is 500 mg/kg while in pork is 2700 mg/kg in, or anserine is present in higher concentration in the chicken muscle (Purchas & Busboom, 2005; Young et al., 2013).

There are reports on peptides extracted from collagen, in an experimental study porcine collagen was treated with pepsin and then the derived hydrolysate was treated with

papain, protease from bovine pancreas (PP) and a cocktail of three enzymes (PP, bacterial proteases from *Streptomyces* and *Bacillus polymyxa*). Results indicated that the hydrolysate which was treated with cocktail of three enzymes showed the highest level of antioxidant activity, and four antioxidant peptides were extracted from this hydrolysate (B. Li et al., 2007). In an another study a 36-amino acid residue peptide was isolated from bovine tendon collagen  $\alpha 1$ , that was able to scavenge free radical and chelate metals (Banerjee et al., 2012).

It is noteworthy that regarding the antioxidant peptides, protein quality and its amount, as well as cost of the raw materials are important for finding the cost benefit peptide. Thus, economical and available materials containing a high amount of protein may feasibly be used to prepare the antioxidant peptides (Tadesse & Emire, 2020).

Another parameter that should be taken into account in antioxidant activity is the ability of the peptide in chelating of pro-oxidative metals such as zinc, copper, and cobalt. The type of complex and bound of peptide and metal ion is important and eventually induce different biological function (Baltic et al., 2014; Young et al., 2013).

### **3.1.2 Bioactive peptides against glutamate excitotoxicity and cell death signaling**

Glutamate excitotoxicity is another mechanism of neuronal cell death induced by oxidative stress in neurodegenerative disease such as AD and PD (Swerdlow, 2012). In physiological condition, transmission of glutamate is associated to energy stability, thus impairment of energy metabolism leads to neuronal cell damage. Moreover, accumulation of glutamate and unnecessary stimulation of its receptors leads to cell death through different mechanisms including ROS generation, mitochondrial

dysfunction, and overload of calcium. In pathological condition excessive release of glutamate into the synaptic space stimulates glutamate receptors of N methyl-D-aspartate (NMDA), which in turn leads to an influx of calcium and sodium and eventually depolarization of the postsynaptic neuron (Q. J. Wu & Tymianski, 2018).

It has been demonstrated that a peptide blocking the interaction of death-associated protein kinase 1 (DAPK1) with glutamate receptor is called NR2B, protects against neuronal death in mice (Tu et al., 2010). In addition, it has been reported that cell permeable peptides including the major calpain cleavage site, is able to prevent the excitotoxicity through attenuating Kidins 220 calpain processing, the mechanism is related to the NMDA receptor toxicity pathway (Gamir-Morralla et al., 2015).

It is well known that over-stimulation of presynaptic N-methyl-D-aspartate (NMDA) receptors triggers and supports glutamate release, while postsynaptic NMDA receptors are responsible for the subsequent apoptotic cascade (Centeno et al., 2007). Previously we found that presynaptic c-Jun N-terminal kinase 2 (JNK2) specifically controls NMDA-evoked glutamate release (Nisticò et al., 2015) and recently we demonstrated that an interaction between Syntaxin-1a and JNK2 is essential to this mechanism. Therefore, we designed and produced a new cell permeable peptide, "JGRi1", a 26 amino acid cell permeable peptide. The 12 residues (GRKKRRQRRRPP) of the HIV-1 Tat protein that confer cell permeability have been linked to the effector portion (IEQSIEQEEGLNRS) as a part of the N-terminal amino acid sequence of STX1a which correspond to the part of the minimal contact area with JNK2. This peptide could block the JNK2/STX1a interaction specifically, and was able to prevent the presynaptic NMDA receptor signaling. JGRi1 diminishes the NMDA-evoked glutamate release both in in-vitro and

ex-vivo experiments while also being able to widely diffuse throughout brain tissue via intraperitoneal administration. In this study we concluded that, JGRi1, acts as a pharmacological tool that promotes neuroprotection (Marcelli et al., 2019).

There are several reports indicate that peptides from natural sources have been reported to interact with key factors in apoptosis, programmed cell death, like Bax and Bcl-2 protein, caspases, as well as factors involved in DNA fragmentation (Chen et al., 2015; Jin et al., 2013). A small 24 amino acids peptide which is called Humanin (HN), was able to inhibit the binding of amyloid beta ( $A\beta$ ), a known AD inducer, to the death receptors and eventually inhibited the neuronal cell death induced by proteins related to AD genes (Harada et al., 2004; Hashimoto et al., 2001). In addition, peptides contain Gly-Pro-Arg and Arg-Glu-Arg can inhibit the neuronal cell death induced by  $A\beta$  through counteracting  $A\beta$ -induced activation of the caspase 3 and p53 pathways (Mileusnic et al., 2004). The peptide Met-Gln-Ile-Phe-Val-Lys-Thr-Leu-Thr-Gly blocked the cytochrome C release and controlled expression of the genes involve in apoptosis such as those encoding cleaved caspase-3, Bax or iNOS (Kim et al., 2010). In addition, hydrophobic whey protein hydrolysates not only increased Bcl-2 (an anti-apoptotic protein) but also were able to decrease the intracellular calcium levels, caspase-3 expression, and PARP cleavage (Jin et al., 2013). The MQIPVLTLTG peptides isolated from venison protein and hydrolysates extracted from lantern fish, plant, and egg proteins showed to prevent apoptosis in *in vitro* studies (Kim et al., 2010; W. Li et al., 2016).

### **3.1.3 Bioactive peptides and modulation of gut microbiota**

Several lines of evidence indicate that altering the regular diet by influencing on the microbiota-gut-brain axis affects neurodegenerative diseases (Gubert et al., 2020). It is well known that the composition of diet plays a key role in the health of the gut as well as the gut microbiota composition and balance which affects the mutual signaling between the gut and brain (Wang et al., 2018). In this area, it has been recently reported that cognitive dysfunction, and inflammation in older people could be improved using Mediterranean diet as a gut microbiota modulator (Ghosh et al., 2020). Nagpal and colleagues, using a modified Mediterranean-ketogenic diet, modulated the composition of gut microbiota and their metabolites which were associated with improved Alzheimer's disease biomarkers in patients cerebrospinal fluid (Nagpal et al., 2019). In addition, there are some peptides able to relieve the symptoms of neurodegenerative diseases. For example, peptides isolated from sesame cake (PSC) enhanced anti oxidative stress, by reducing the ROS levels, and A $\beta$  deposition in a transgenic *Caenorhabditis elegans* model of AD. This mechanism might be contribute to delay AD onset in this model (Ma et al., 2017). Also, PSC significantly decreased the  $\alpha$ -synuclein aggregation in a PD *C. elegans* model, indicated that PSC, as a beneficial tool, ameliorated PD-related pathologies (Ma et al., 2020). Therefore, peptides obtained from the proteins digestion in diet or consumed as supplements can contribute to the gut homeostasis by regulating the gut microbiota and ROS homeostasis.

Peptides may improve the dysbiosis of gut homeostasis through modifying the gut ROS level. In fact, the imbalance between ROS amount and antioxidant systems leads to apoptosis and also affects gut microbiota, which have been shown to be associated with neurodegenerative disease (Cryan et al., 2019; Dumitrescu et al., 2018).

Moreover, peptide treatment increased some gut probiotics (Z. Zhang et al., 2020). These probiotics can produce various metabolites with antioxidant activity, like glutathione, folate, and butyrate, and eventually are able to protect the host against oxidative stress injury through eradicating ROS accumulation (S. Wu et al., 2021).

Taken together, several lines of evidence indicating that alteration in gut microbiota can change the enteric and peripheral inflammatory pathways, which in turn induce neuroinflammation and neurodegeneration (Pellegrini et al., 2018, 2020; S. Wu et al., 2021), therefore targeting this pathway using some peptides in diet could be a helpful approach to prevent neurodegenerative disease.

#### **3.1.4 Bioactive peptides against inflammation**

Inflammation is the physiologic response to the damage which is characterized by augmented endothelial permeability and infiltration of leukocytes into extravascular tissues. Neuroinflammation is a defensive process that initially can protect the central nervous system by eliminating or preventing various pathogens (Wyss-Coray & Mucke, 2002). Therefore, it has beneficial effects via inducing tissue repair and removing cellular debris (Russo & McGavern, 2016). However, excessive and uncontrolled inflammatory process often leads to chronic diseases. Endogenous factors such as genetic mutation and protein aggregation or environmental stimulus like trauma, infection, and drugs might be the reasons for persistence of inflammatory responses (Glass et al., 2010) which may lead to neurodegenerative diseases (Kempuraj et al., 2016).

Neuroinflammation is a major mechanism involved in the onset and progression of several neurodegenerative disorders like AD and PD. In fact, it is responsible for an

abnormal secretion of proinflammatory cytokines induce signaling pathways contribute in neurodegeneration. Once the inflammatory cascade activated by damage signals, the synaptic dysfunction occurs through several molecular mechanisms. This process generates a positive feedback mechanism promoting even more cellular damage and death (Guzman-Martinez et al., 2019).

Gut inflammation is another mechanism to induce an immune response and inflammatory processes which could contribute to neurodegenerative disease like PD pathology (Guzman-Martinez et al., 2019).

In recent decades peptides and protein hydrolysates derived from food sources like meat, egg, milk, fish, and soybeans (to name a few) have all been evaluated for their potential beneficial effects on immune system and inflammation. For instance, bioactive peptides from milk as a rich source of caseins and whey proteins, have been tested for this purpose. The tripeptides, Val-Pro-Pro(VPP), has been reported to have the ability of reducing leukocyte-endothelial interactions, mainly through inhibition of proinflammatory c-Jun N-terminal kinase (JNK), a member of MAP kinase superfamily, pathway (Aihara et al., 2009). Casein hydrolysates obtained through enzymatic digestion have also been evaluated for anti-inflammatory properties. For example, digestion of casein with Corolase, produces compounds exerted anti-inflammatory effects on activated macrophages (Nielsen et al., 2012). It has been reported that, milk contains transforming growth factor-beta (TGF-beta), IL-10, and immunoglobulins, a number of anti-inflammatory and immunomodulatory agents (Rutherford-Markwick, 2012). Moreover, tripeptides (IRW and IQW) obtained from ovotransferrin (an egg white component) were able to down regulate the cytokine-induced inflammatory protein

expression in vascular endothelium, by modulating of NF- $\kappa$ B pathway (Majumder et al., 2013). In an *in vitro* study Fitzgerald and colleagues showed that a fish hydrolysate preparation could induce proliferation and migration in intestinal epithelial cells, which may contribute to anti-inflammatory and healing properties (Fitzgerald et al., 2005).

## Conclusion

Currently, people and governments all over the world are concerned about the rapid progress of non-communicable diseases, such as cancers, diabetes, cardiovascular and neurodegenerative disease. Therefore, the interest to the health-promoting foods has been dramatically raised. Based on the evidence reviewed here we think that bioactive peptides isolated from food sources are reasonable tools to counteract oxidative stress, apoptosis and cell death pathway, inflammation and eventually neurotoxicity. Although these compounds are promising as the potential anti-neurodegenerative agents, further investigations are needed to understand their pharmacokinetic/dynamics and to clarify these beneficial effects in order to effectively translate the research on the bench to the bedside.

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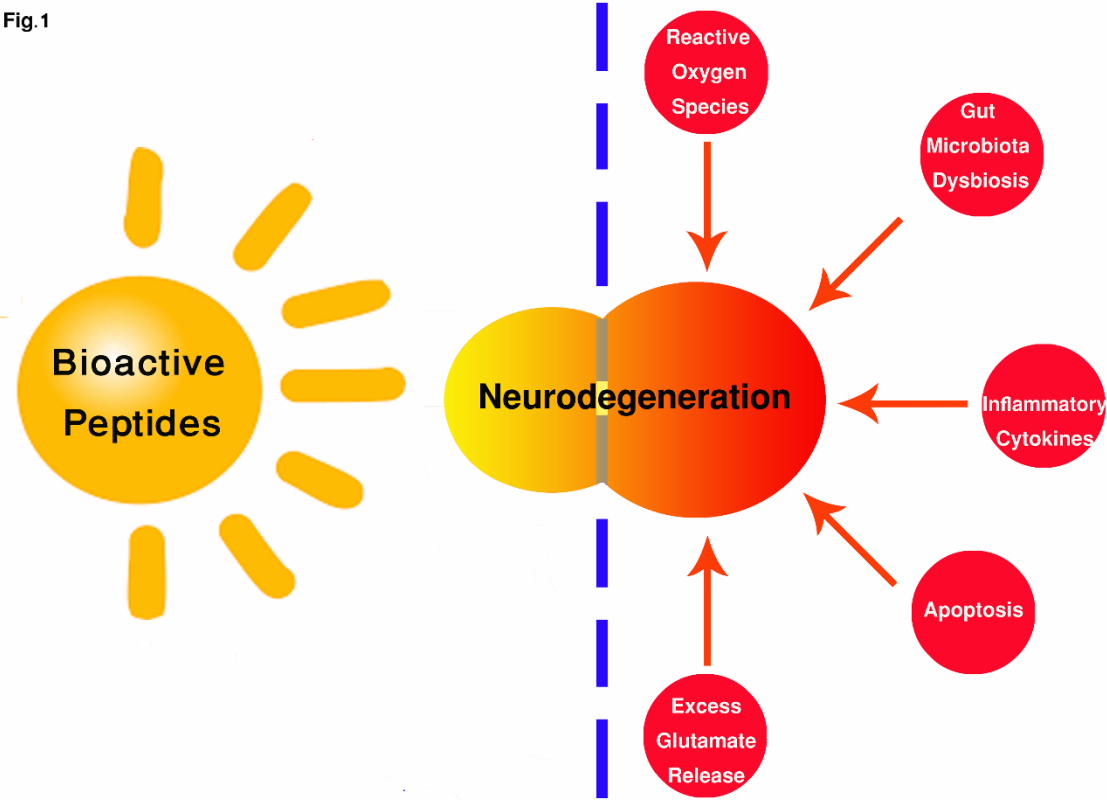
**Table. 1** Classification of neurodegenerative disease

Category	Disease type	Protein(s) involve	Brain affected area (Dugger & Dickson, 2017; Ganguly & Jog, 2020a; Reiner et al., 2011)
α-Synucleinopathy (McCann et al., 2014)	Parkinson's disease (PD)	α-Synuclein	Basal ganglia including: Caudate nucleus Putamen Globus pallidus Subthalamic nucleus Substantia nigra
	Dementia with Lewy bodies (DLB)	α-Synuclein	Amygdala Cerebral cortex Dorsal motor nucleus Hippocampus (CA2) Locus coeruleus Olfactory bulb Substantia nigra

	Multiple system atrophy (MSA)		$\alpha$ -Synuclein	Putamen Substantia nigra Pontine nuclei Medulla (inferior olivary nucleus) Cerebellum
Tauopathy (Ganguly & Jog, 2020b)	Primary	Progressive supranuclear palsy (PSP)	Tau	Subthalamic nucleus Substantia nigra Superior colliculus Cerebellar dentate
		Corticobasal degeneration (CBD)	Tau	Frontoparietal association cortices Neostriatum Substantia nigra
		Argyrophilic grain disease (AGD)	Tau	Limbic structures
		globular glial tauopathy (GGT)	Tau	Frontotemporal cortices
		Pick disease (PiD)	Tau	Basal forebrain Frontal and temporal lobes Limbic structures Striatum
		Neurofibrillary tangle (NFT)-dementia or primary age-related tauopathy, PART	Tau	medial temporal lobe, particularly the hippocampal formation and adjacent regions
	Secondary	Alzheimer disease (AD): Secondary to Amyloid deposition	Tau, A $\beta$	Basal forebrain Frontal and temporal lobes Limbic structures Locus coeruleus Olfactory bulb
		Chronic traumatic encephalopathy (CTE): Secondary to repeated trauma	Tau	Cortical sulci
TDP-43 Proteinopathy (Brettschneider et al., 2015)	Frontotemporal lobar degeneration (FTLD)-TDP		TDP-43	Frontal and temporal cortices Basal ganglia Substantia nigra
	Amyotrophic lateral sclerosis (ALS)		TDP-43	Motor cortex Brainstem motor neurons Spinal cord motorneurons
FUS Proteinopathy (Brettschneider et al., 2015)	Frontotemporal lobar degeneration (FTLD)-FUS		FUS	Motor cortex Brainstem motor neurons Spinal cord motor neurons
	Amyotrophic lateral sclerosis (ALS)			

Huntington's disease	Huntington's disease	Huntingtin	neocortex, entorhinal cortex, subiculum, hippocampal pydamidal neurons, and striatum
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Fig.1



**Figure 1.** Bioactive peptides counteract different pathways involved in neurodegeneration.