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Review Article

Peptides Therapy for Neurodegenerative Disorders

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Abstract

Recent research has increasingly highlighted the pivotal role in the pathogenesis and progression of neurodegenerative diseases (NDDs). Peptide deficiency has emerged as a significant factor influencing disease progression in NDDs, underscoring the importance of understanding the interplay between peptides and diseases. In the realm of NDDs, where effective treatments remain elusive, peptide therapies have garnered attention for their potential to modify disease progression. Recognized for their disease-modifying properties, peptide therapies offer promising avenues for intervention in NDDs This paper aims to provide a comprehensive overview of the pathogenesis of NDDs such as Parkinson's disease and Alzheimer's disease, as well as an analysis of how altered levels of peptides, particularly vasoactive intestinal peptide, glucagon-like peptide, glutathione, cholecystokinin, and neurotensin, contribute to the development of these diseases. Through elucidating the role of peptides in NDDs, this review paper seeks to explore their potential as therapeutic targets for the treatment of these debilitating conditions.

Background

Peptides are signaling molecules composed of short amino acid sequences that can bind to specific receptors, for example, to trigger intracellular effects [1]. They are ubiquitous in all eukaryotic organisms, including hormones, neurotransmitters, growth factors, ion channel ligands, etc., and play an extremely important role in biological activities [1,2]. Peptides have been used in the treatment of disease for nearly a century, since the advent of insulin therapy [3]. Due to their low toxicity, better tumor penetration, and good biocompatibility, peptides have made tremendous progress in recent decades and have shown excellent therapeutic efficacy [4]. Currently, numerous peptides are in clinical use, with hundreds more undergoing preclinical studies [2], particularly in the fields of cardiovascular and cerebrovascular diseases, diabetes, and cancer [5-7]. *Chan, et al*. summarized the anti-aging effects of thymic peptides [8], and *Wellington, et al*. found a therapeutic role for peptide therapy in older canines [9]. The study by *Roni, et al*. suggests that peptides therapy may have a therapeutic effect on autoimmune diseases such as non-specific interstitial pneumonia [10]. All of the above studies demonstrate the superior therapeutic effects of peptides. Similarly, recent studies have shown that peptides may have some therapeutic effects on neurodegenerative diseases (NDDs) [11]. For example, Klokol *et al*. demonstrated the neuroprotective effects of mitochondria-produced small humanin like peptides (SHLP), which protects the brain from degenerative diseases [12]. In this paper, we have reviewed the peptides currently available for the treatment of NNDs, aiming to provide assistance for the management of these disorders.

Neurodegenerative Disorders

Parkinson's Disease

Parkinson's disease (PD) is one of the most prominent neurodegenerative disorders, with a progressive increase in risk as people age [13]. The prevalence of PD has steadily increased over the last few decades, affecting up to 6 million people globally [14], with projections suggesting it may reach 10 million by 2030 [15]. The onset of PD is associated with nigrostriatal degeneration and striatal dopamine depletion [16,17]. However, the definitive cause and pathogenesis of PD remain unclear [18]. It has been reported that 90% of patients have no identifiable genetic cause [19]. PD is currently defined as bradykinesia with resting tremor or rigidity [20]. Patients with PD may also present with a long prodromal period characterized by deviations in recollection, with the main symptoms being decreased sense of smell and sleep disturbances [21]. Movement disorders lead to progressive disability, impaired daily activities, and reduced quality of life.

To date, no drug has been demonstrated to definitively mitigate the progression of PD [22]. Current treatments provide only temporary symptomatic relief and neuronal loss is not restorable [23]. The most common option is pharmacologic, specifically oral levodopa, to alleviate the patient's symptoms [24]. Additional oral medications include dopa decarboxylase inhibitors, non-ergot dopamine agonists, and monoamine oxidase inhibitors [25]. Other therapies also exist, such as surgical interventions involving deep brain electrical stimulation [26] and cellular therapies like fetal midbrain dopamine neuron transplantation and stem cell transplantation [26,27]. Despite the variety of therapies currently available, none of them have proven capable of slowing down the progression of PD. Consequently, there is an urgent need to explore novel therapeutic modalities with the potential to decelerate or even cure PD.

Alzheimer's Disease

Alzheimer's disease (AD) is the most important cause of dementia, which is characterized by progressive amnesia and is often accompanied by psychiatric disorders, which severely affect personal activities and are an important cause of disability and mortality [28,29]. The disease currently affects approximately 50 million individuals worldwide, with projections indicating that this number will reach 100 million by 2050 [30]. AD is characterized by the presence of amyloid plaques, which are often found on the surface of the body. These plaques are associated with the formation of neurofibrillary tangles, which have been linked to a reduction in the synthesis and release of acetylcholine. This, in turn, has been shown to lead to synaptic degeneration and neuronal atrophy [28,31]. Similarly, there is no cure for Alzheimer's disease, and only symptoms are treated with acetylcholinesterase inhibitors (e.g. galantamine) and N-methyl-D-aspartate (NMDA) receptor antagonists (such as memantine) [32,33]. These drugs may help reduce or control some cognitive and behavioral symptoms. Additionally, stem cell therapy has emerged as a possible treatment for AD, with research suggesting that stem cells can improve cognitive function and reduce the symptoms of the disease [34]. However, the benefits of long-term treatment are limited or unclear. More therapeutic options are to be investigated.

In summary, both PD and AD are charactetized by the degeneration of the specific neuronal cells producing some peptides such as neuromediators dopamine (PD) or acetylcholine (AD). It allows to classify the changes in PD and AD patients as neurodegenerative.

Other types of NDDs

Huntington's Disease: Huntington's disease (HD) is an inherited NDD caused by a repetitive amplification of the Cytosine, Adenine, Guanine (CAG) repeat of the Huntingtin gene located on the short arm of chromosome 4. Mutations in the gene produce mutant Huntington's protein [35]. Nonetheless, the etiology of HD remains uncertain, and HD is characterized by neuropsychiatric symptoms, movement disorders, and dementia [36]. These symptoms are mainly characterized by chorea and loss of coordination, but also by psychiatric symptoms such as depression and obsessive-compulsive disorder (OCD) [37]. These symptoms greatly affect the lives of the patients. Due to its chromosomal characteristics, HD is easier to be diagnosed than other disorders, but the treatment is still scarce. Current treatments for the condition include symptomatic medications such as antipsychotics and antidepressants to alleviate psychiatric symptoms [38] and medications like tetrabenazine to manage chorea [39]. Additionally, therapies such as antisense nucleotide therapy and gene therapy are being explored [40]. Despite the increased awareness of HD in recent years, advances in basic science understanding have not yet translated into effective disease-mitigating therapies.

Amyotrophic lateral sclerosis: Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease, is a fatal neurodegenerative disease of the central nervous system. It is characterized by degeneration of the upper and lower motor neurons, which leads to muscle weakness and eventual paralysis. Initially, this is manifested as predominantly limb symptoms [41]. As the disease progresses, it can gradually affect swallowing, speaking and even breathing, which can become life-threatening [42]. Cognitive and behavioral changes are also noted in some patients during the early stages of the disease [43]. The pathogenesis of ALS remains uncertain, while skeletal muscle atrophy and motor neuron reduction have been observed [41]. Currently, treatments for ALS consists of medications like riluzole and edaravone, which are usually less effective, along with symptomatic therapies.

Multiple Sclerosis: Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that can lead to demyelination and neurodegeneration [44]. Similar to above-mentioned diseases, the mechanism of this disorder is also unclear. It is now generally considered that MS is genetically determined and influenced by environmental factors. Recurrent attacks may occur, with complete or partial recovery between attacks, manifesting as a relapsing-remitting phenotype [45]. The symptoms of MS vary depending on the system involved and may include spasticity, dyskinesia, fatigue and ataxia [46]. The treatment of MS can be divided into three categories: acute relapsing-remitting treatments (e.g. high-dose methylprednisolone), ameliorative treatments (e.g. immunosuppressive drugs), and symptomatic treatments. However, overall, each of these categories struggles to halt the progression of the disease [45,47].

NDDs are typically associated with genetic factors, yet their underlying mechanisms remain poorly understood, and conventional treatments are often ineffective in curing or slowing disease progression. Therefore, the development of novel therapies for NDDs is of particular importance.

Peptides in NDDs

As previously stated, peptide imbalance in the body is involved in the initiation and advancement of NDDs. The ensuing section will delineate several peptides that hold notable significance within this framework.

Vasoactive Intestinal Peptide

Vasoactive intestinal peptide (VIP) is a type of neurotransmitter comprising 28 amino acids. It is primarily released by intestinal neurons [48], and widely distributed throughout the central and peripheral nervous systems, as well as multiple organs. VIP is both a gastrointestinal hormone and a neuropeptide. There is now growing evidence showing that altered VIP expression and signaling is found in multiple NDDs [49]. Consequently, VIP may represent a promising therapeutic target for the treatment of various NDDs.

VIP and PD: The neuroprotective effects of VIP have been demonstrated *in vitro* and *in vivo*, preventing neuronal cell death [50]. Consequently, it is postulated that VIP may have a role in the treatment of PD. In an experiment in which VIP was administered systemically to a rat model of PD, researchers found that VIP significantly improved motor deficits but not dopamine levels in rats [51]. In another study, *Delgado, et al*. demonstrated that VIP treatment reduced dopaminergic neuron and nigrostriatal nerve fiber deficits in mice [52]. However, it has been shown that VIP neurons in PD patients have no effect on the dopaminergic neurons [53]. This finding suggests that while VIP has potential, it may not serve as a standalone therapeutic option for dyskinesia in PD patients. Further studies are necessary to explore the potential utility of VIP in PD treatment.

VIP and AD: VIP is able to limit the release of neurotoxins produced by β-amyloid-induced activation of microglia, thereby reducing neuronal death [54]. An experiment based on a mouse AD model demonstrated that chronic intraperitoneal administration of VIP significantly reduced Aβ accumulation and atrophy in brain regions involved in cognition, such as the hippocampus and cortex [55]. In another *in vivo* experiment, *Song, et al*. found that VIP overexpression attenuated amyloidosis in transgenic APP/PS1 mice [56]. Therefore, it may be hypothesized that VIP represents a potential therapeutic agent for cognitive dysfunction in AD. Clinical data are needed to validate this potential.

VIPs and other NDDs: The relationship between VIP and HD remains inconclusive. Some researchers observed reduced VIP receptor expression in the hippocampus of HD mouse models [57]. Additionally, studies of human autopsies showed decreased VIP in the amygdala immunoreactive central nucleus [58]. However, the level of VIP protein in the prefrontal cortex and basal ganglia did not change [59]. Recently, it has been reported that VIP does not stimulate the expression of c-fos, egr1, CBP, and the neurotrophic factor BDNF in STHdh cells, which may be ineffective in the treatment of HD [60]. In patients with ALS, Werdelin *et al*. observed a reduction in VIP levels in cerebrospinal fluid [61]. In ALS rats, Goursaud *et al*. found that modified VIP mimics exert anti-inflammatory effects, improving motor function and prolonging lifespan [62]. These results indicate a potential therapeutic benefit of VIP in ALS.

Glucagon-like peptide (GLP)

Glucagon-like peptide (GLP-1) is a hormone produced primarily by intestinal L cells. GLP-1 stimulates enhanced insulin secretion and inhibits glucagon secretion, and has therefore been recognized as a novel hypoglycemic agent in recent years [63,64]. Due to its ability to cross the blood-brain barrier, GLP-1 and its receptor are widely expressed in the central nervous system [65]. The hypoglycemic mechanism of GLP-1 stems from its capacity to resensitize cellular signaling to insulin [64]. Previous studies have demonstrated the presence of insulin desensitization in the brains of patients diagnosed with PD and AD [66,67]. Moreover, insulin resistance has been linked to the neuropathological features of PD, including α-synuclein aggregation, dopaminergic neuron loss, neuroinflammation, mitochondrial dysfunction, and autophagy [68]. These factors have also been identified as potential contributors to the pathogenesis of AD. Therefore, GLP-1 may be a promising therapeutic target for PD and AD.

GLP in NDDs

Some researchers have found that GLP-1 analogs can protect nigrostriatal dopamine neurons from death and dopamine depletion [69]. GLP-1 receptor (GLP-1R) activation protects nigrostriatal neurons and replenishes dopamine production in PD patients [70]. In a rat PD model, *Zhang, et al*. demonstrated that the use of GLP-1 reduces the level of apoptotic effector cysteine asparaginase 3 in the substantia nigra striata brain region [71]. This neuroprotective efficacy suggests that GLP-1 may be a potential molecule for PD treatment.

GLP-1 also has great potential in the treatment of AD. *In vitro* experiments showed that GLP-1 analogs can rescue the downregulation of synaptic proteins and synaptic densities driven by Aβ oligomers in a GLP-1R- and cAMP/PKA-dependent manner [72]. Additionally, GLP-1 has been shown to promote neurite growth [73] and prevent the accumulation of β-amyloid in the body [74].

In the context of ALS, GLP-1 holds promise to serve as a therapeutic agent. Previous studies have shown that dysregulation of the insulin-like growth factor-1 (IGF-1) and GLP-1 pathways can result in the destruction of oligodendrocytes, the overactivation of microglia, an imbalance in the immune system, inflammation of neurons, and an increase in neural excitability, which collectively contribute to the demyelination observed in ALS [75]. In a mouse study, Sarah and colleagues demonstrated that injecting GLP-1-derived mesenchymal stem cells (MSCs) into the lateral ventricle improved motor performance and survival [76]. Conversely, Keerie *et al*. present an opposing argument, suggesting that GLP-1 does not slow disease progression in a transgenic mouse model of ALS [77].

Recent studies demonstrated that GLP-1R agonists exert neuroprotective effects through anti-inflammatory, anti-inflammatory

vesicle activation, and anti-apoptotic mechanisms [78]. *Song, et al*. observed in experimental autoimmune encephalitis (EAE) mice that GLP-1R improved the mice's condition and reduced the central nervous system (CNS) inflammation and demyelination [79]. Furthermore, Hardonova *et al*. demonstrated that GLP-1 agonist administration attenuated very-low-density lipoprotein (VLDL) levels and enhanced vascular endothelial function in MS patients [80], indicating that GLP-1 agonist exerts an attenuating effect on vascular risk in MS patients. These studies suggest that GLP-1 analogs may be a promising treatment option for multiple sclerosis.

Glutathione (GSH)

Glutathione (GSH) is a tripeptide that was first identified over a century ago [81]. It exerts antioxidant effects and protects the body from oxidative stress-induced damage by reducing reactive oxygen species [82]. GSH plays a crucial role in maintaining normal immune system function, making it pivotal in the neuronal antioxidant defense system and the maintenance of redox homeostasis [83]. A deficiency of GSH has been found in several NDDs such as AD, PD and ALS. Consequently, it is regarded as a potential therapeutic target for these disorders.

Despite its considerable potential, GSH as a drug still has certain drawbacks, including a relatively short half-life and an insufficient ability to penetrate cell membranes. These limitations may restrict its clinical application [84]. However, the application of N-acetylcysteine (NAC; the precursor of glutathione) may compensate for this shortcoming.

GSH in NDDs

In a study by Charisis and colleagues, it was found that elevated plasma GSH levels were associated with a lower incidence of prodromal PD [85]. In a separate study by Chinta *et al*., reduced GSH under *in vitro* conditions resulted in neuronal cell loss and nigrostriatal degeneration [86]. *Jurma, et al*. demonstrated that the depletion of GSH in PC12 cells reduced dopamine uptake, suggesting its potential involvement in the progression of PD [87]. *Aoyama, et al*. reported that GSH deficiency led to oxidative stress in the midbrain using a mouse model of PD [88]. Furthermore, the use of NAC has been found to not only easily cross the blood-brain barrier [89] but also to increase GSH content, thereby reducing neurotoxicity [90], reducing synaptic connections in the brain [91], and attenuating apoptosis in melanocytes of PD patients [92]. This indicates that the damage to brain tissue resulting from GSH deficiency is potentially reversible.

Chiang, et al. demonstrated a negative correlation between GSH levels and amyloid β levels in the temporal and parietal lobes of healthy older adults [93]. In contrast, hippocampal glutathione levels were significantly lower in AD patients compared to healthy elderly controls, and the decline in GSH was associated with cognitive impairment [94]. Furthermore, NAC has been shown to inhibit β-amyloid-induced apoptosis in cortical neurons [95], thereby providing addition evidence of GSH's role in AD pathogenesis.

Fontaine, et al. illustrated that NAC alleviated the increased oxidative stress observed in rat striatum and cortical synaptosomes induced by nitropropionic acid [96]. Similarly, Stanislaus *et al*. revealed that NAC reversed 3-nitropropionic acid (3-NP) -induced mitochondrial dysfunction and neurobehavioral deficits, suggesting its therapeutic role in HD [97].

CCK in NDDs

Cholecystokinin (CCK) is a polypeptide hormone with a function to stimulate the secretion of gastric juice and bile from the gastrointestinal tract [98]. It has been decades since CCK was discovered as a neuromodulator [99]. In brain neurons, CCK is predominantly sulfated, resulting in the formation of CCK-8, or CCK-8S [100]. CCK-8S is highly expressed in the hippocampus [101], and its receptor is also highly expressed in this region [102]. This suggests that CCK-8S may be involved in memory formation as well as AD [103]. Brain CCK levels have been shown to decrease in AD patients, with a demonstrated inverse relationship to the degree of cognitive impairment [104,105]. In addition, CCK may inhibit AD progression by stimulating hippocampal neurogenesis [106], inhibiting chronic inflammation [107], and restoring insulin resistance [104]. CCK also holds therapeutic promise for PD. Its anti-inflammatory and anti-apoptotic effects contribute to mitigating synaptic degeneration and the loss of dopamine neurons in the substantia nigra, leading to improved motor function. Additionally, CCK-8 can stimulate striatal dopamine release [108]. However, studies have indicated that CCK-8 administration fails to improve motor function in PD patients [109]. Further research is warranted in the future.

Neurotensin in NDDs

Neurotensin (NTS) is a neuropeptide known for its notable antihypertensive effects and is present in neural tissues. NTS has an excitatory effect on many neurons, including those in the substantia nigra, medial prefrontal lobe, hypothalamus and central gray matter. NTS levels in the hippocampus of patients with PD are found to be significantly lower than those of healthy subjects [110]. *Lazarova, et al*.'s research in animal models revealed that NT2 and NT4, analogues of NTS, can easily cross the blood-brain barrier and increase dopamine levels in the brains of PD rats following intraperitoneal drug injection [111]. A study by *Antonelli, et al*. demonstrated that NTS enhances glutamate outflow in the striatum, substantia nigra, and cortex, suggesting a potential therapeutic effect on PD through the enhancement of NMDA receptor function [112]. *Gahete, et al*. found significant reductions in NTS receptors in the temporal lobe of AD patients [113]. *Xiao, et al*. observed that administering NTS receptor agonists significantly improved memory in APP/PS1 mice [114]. These studies indicate a potential involvement of NTS in the pathogenesis of AD.

Conclusion

Peptides are intricately linked to NDDs. Over the past decades, researchers have tirelessly pursued understanding the pathogenesis of NDDs through extensive basic studies and clinical trials targeting peptides for treatment. This endeavor has led to the development of several marketed peptide-based drugs. However, the complexity of NDD mechanisms remains beyond our current understanding. Further investigation is needed to elucidate their mechanisms of action, and scientists must explore novel formulations and delivery methods to optimize the functionality of peptides.

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