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Review

Peptide based therapeutics and their use for the treatment of neurodegenerative and other diseases

Mohammad Hassan Baig[a,*], Khurshid Ahmad[a], Mohd Saeed[b], Ahmed M Alharbi[b], George E. Barreto[c,d], Ghulam Md Ashraf[e], Inho Choi[a,*]

[a] Department of Medical Biotechnology, YeungNam University, 280 Daehak-ro, Gyeongsan, Gyeongbuk, Republic of Korea
[b] Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, University of Hail, KSA, Saudi Arabia
[c] Departamento de Nutrición y Bioquímica, Facultad de Ciencias, Pontificia Universidad Javeriana, Bogotá D.C, Colombia
[d] Instituto de Ciencias Biomédicas, Universidad Autónoma de Chile, Santiago, Chile
[e] King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia

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ABSTRACT

Bioactive peptides are actively involved in different biological functions and importantly contribute to human health, and the use of peptides as therapeutics has a long successful history in disease management. A number of peptides have wide-ranging therapeutic effects, such as antioxidant, antimicrobial, and antithrombotic effects. Neurodegenerative diseases are typically caused by abnormal aggregations of proteins or peptides, and the depositions of these aggregates in or on neurons, disrupt signaling and eventually kill neurons. During recent years, research on short peptides has advanced tremendously. This review offers a brief introduction to peptide based therapeutics and their application in disease management and provides an overview of peptide vaccines, and toxicity related issues. In addition, the importance of peptides in the management of different neurodegenerative diseases and their therapeutic applications is discussed. The present review provides an understanding of peptides and their applications for the management of different diseases, but with focus on neurodegenerative diseases. The role of peptides as anti-cancer, antimicrobial and antidiabetic agents has also been discussed.

1. Introduction

Today peptide-based drugs have emerged as a major class of therapeutics as a result of extensive research conducted at biotech and pharmaceutical companies. This journey started with the discovery of oxytocin in 1953, which was the first synthetic peptide based therapeutic agent. In 1974, recombinant DNA technology enabled the production of therapeutic peptides at industrial levels, and human insulin was the first approved therapeutic peptide synthesized in this manner. In recent decades, great advances in synthetic peptide technologies have occurred, which has encouraged pharmaceutical industries and researchers to identify peptides of clinical utility and overcome obstacles preventing commercialization. A number of therapeutic peptides, both natural and synthetic analogs, are undergoing clinical trials [1]. The last decade has witnessed unprecedented scientific and industrial interest in the use of peptides as therapeutics [2].

Peptides have a number of advantages over small molecules, such as high specificity, high biological activity, low cost and high membrane penetration ability [3,4]. However, stability, toxicity, and immunogenicity remain primary concerns of those developing peptide-based drugs. Various routes have been devised to enhance the stabilities of peptides, such as the integration of D-amino acids (increases protease resistance) or α-aminoxy amino acids, altering backbone chemistry, and cyclization [5–7]. However, these incorporations tend to reduce the storage stabilities by making peptides sensitive to temperature and pH. The utilization of proteins and peptides as therapeutic agents is hindered by a complex set of inherent properties associated with their complex spatiotemporal physicochemical natures, which are invariably foreign to receiver organisms.

Neurodegenerative disorders (NDs) are marked by a gradual loss of neurons within the brain, eventually leading to death. In fact, it has been estimated that a major proportion of global deaths and disabilities (~25%) are caused by brain-associated disorders [8,9], such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease

Abbreviations: NDs, Neurodegenerative disorders; AD, Alzheimer's disease; PD, Parkinson's disease; SPPS, Solid-phase peptide synthesis; NAC, N-acetylcarnosine; ACP, santicancer peptides; RBCs, red blood cells

* Corresponding authors.
E-mail addresses: mohdhassanbaig@gmail.com (M.H. Baig), inhochoi@ynu.ac.kr (I. Choi).

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(HD) and amyotrophic lateral sclerosis (ALS) [10,11]. The available treatments for managing NDs are insufficient, and the number of drugs approved is limited by the high failure rates of lead compounds in clinical trials [12]. Peptides are vital tools for ND research studies and can be used to study the properties of misfolded proteins and/or peptides. Here, we discuss the successful application of synthetic peptides and their natural counterparts in drug discovery along with their drawbacks and limitation. The use of these peptide inhibitors as therapeutic drug candidates is also highlighted. In addition, we discuss the therapeutic utilities and versatilities of peptide inhibitors in various neurodegenerative disorders.

2. Natural peptides

2.1. Carnosine

(β-alanyl-l-histidine) is a dipeptide natural antioxidant that is composed of the amino acids histidine and alanine [13]. Carnosine was first discovered as a non-protein nitrogen-containing compound of meat in the early 19th century. Later, this dipeptide was found in other excitable tissues as well. Expect humans, several other organisms possess either anserine or ophidine/balenine, which are methylated variant of carnosine, and are also collectively termed as histidine-containing dipeptides [14]. It is synthesized and contained in human muscle and nervous tissues, is easily absorbed in the digestive tract, penetrates blood-brain barrier, has high bioavailability, and a strong membrane-stabilizing action [15]. Carnosine is a low molecular weight hydrophilic antioxidant, and also participates in anti-radical protection systems in vivo [16]. Carnosine is present in heart, kidneys skin, brain, muscles, gut, and other tissues. Some of the major dietary food sources of carnosine are beef, chicken, tuna, turkey, rabbit, pork etc. It has been suggested carnosine can be used as a dietary supplement and might be useful to treat diseases, such as Alzheimer's disease [17,18], autism [19], brain ischemia [20], Parkinson's disease [21], Down's syndrome [22], epilepsy [23]), schistosomiasis [24] aging [25–27], and to prevent cataract formation [28]. It was demonstrated in earlier studies that the use of carnosine increases the stabilization of HIF1-α and the mobilization of endothelial progenitor cells, resulting in improved blood flow, and thus can be used as a safe therapy for the treatment of critical limb ischemia patients [29]. Oral supplementation with carnosine significantly increases carnosine levels in skeletal muscles [30], and intracerebroventricular injections of carnosine suppress renal sympathetic nerve activity and blood pressure [31]. When injected intracerebroventricularly, it was found to reduce the food intake in a dose-dependent fashion [32]. A large number of enzymes (such as carnosine dipeptidase II) control carnosine levels in tissues, which convert carnosine into other related substrates, such as anserine, carcinine, and ophidine by various enzymatic reactions like acetylation, decarboxylation or methylation. Carosinase (EC 3.4.13.3) is primarily responsible for the hydrolysis of carnosine to histidine and β-alanine, which is widely distributed in serum and its deficiencies cause a urinary disorder [33].

2.2. Defensins

Defensins are natural peptides with reported broad spectrum antimicrobial activity [34] and have been isolated from the granules of neutrophils of guinea pigs, humans, rabbits and rats. Human defensins are cationic in nature and classified as α- and β-defensins. Both defensins types have molecular weights ranging between 3 and 6 kDa and a triple-stranded β-sheet structure. The main difference between α- and β-defensins involves different pairings of cystine-disulphide bridges. The anti-microbial potencies of defensins vary among microbial species. It has been reported defensins invade enveloped viruses without any toxic effect and hamper tissue cultures [35]. Defensins are also reported of exhibiting anti-HIV-1 activities. The synthetic defensin when used as an antiviral therapy was found to show characteristics indicating its promising role as a therapeutic candidate against HIV-1 [36]. Additionally, defensins are known to play active roles in growth-dependent processes like wound healing and epidermal proliferation. For example, HNP1-3 promotes wound closure in airway epithelial cell cultures [37]. In addition, defensins are viewed as potential skin care agents.

Cathelicidin are the family of antimicrobial peptides which were named cathelicidins because of the presence of a conserved cathelin domain [38]. In 1980, Cecropin was the first cathelicidin isolated from tissues of the Hyalophora cecropia moth [39]. In 1987, Zasloff isolated another member of this family from the skin of the Xenopus leavis frog and this member was named "magainin" [40]. The story goes on and a large number of different cathelicidins were isolated from humans and other organisms like chickens, goats, fish, sheep, horses, pigs and rabbits [38]. Cathelicidin are a group of natural peptides which are cationic in nature and are found to be carrying antimicrobial properties [38]. Cathelicidins are proteolytically activated peptides and in several vertebrates, humans and farm animals they are a major part of the innate immune system. These peptides are widely reported to be carrying a broad spectrum of antimicrobial activity against different bacteria, fungi and viruses [38,41,42].

2.3. Dermcidin (DCD)

Dermcidin (DCD) is a natural antimicrobial peptide that is constitutively secreted by sweat glands and generally transported to the epidermal surface via sweat [43,44]. It is an anionic peptide comprises of 47 residues and one leucine residue (DCL-1L) was reported to be showing broad spectrum antimicrobial activity against pathogenic microbes (fungi and bacteria) at an average concentration of ~10 μg/mL [45]. DCD-1L can assimilate itself into the membrane of bacterial cytoplasm to kill them [46]. DCD expression has also been reported in multiple human tumor types and in gestational tissue, which suggests it acts as a multifunctional active peptide and might be involved in tumorigenesis and the pathophysiologies of pregnancy-related and human innate immune system disorders and neuronal diseases [47,48].

2.4. Hepcidin

Hepcidin is a peptide hormone that has been identified in fish, reptiles, amphibians, birds, and mammals. It is a cysteine-rich 25 amino acid peptide which is initially synthesized as a preprohormone of 84 amino acid, and is later processed in hepatocytes to generate a 60 amino acid prohormone before undergoing processing and finally a 25 amino acid hepcidin [49,50]. The structure of the mature form of Hepcidin hormone is a compactly folded protein with conserved β-sheet structure (32%) and 4 disulphide bonds. This liver-derived peptide is one of the key regulators of systemic iron homeostasis [51]. The secretion of this peptide takes place in response to iron and inflammation [51]. The unbalanced production of this hormone leads to the pathogenesis of various iron disorders. Due to the direct involvement of hepcidin in controlling the iron absorption, the measurement of this hormone is found to be very helpful in the diagnosis of anemia [52,53]. Hepcidin has been shown to have anti-bacterial, anti-viral, and anti-fungal activities [54,55]. Hepcidin controls the iron delivery from intestinal cells, iron-storing hepatocytes and erythrocyte-recycling macrophages to blood plasma, and from all iron-transporting cells [56].

3. Discovery of novel peptides

The majority of the techniques developed to screen and generate pharmacologically active peptides is time consuming and complicated. Conventional drug discovery involving peptide synthesis is a complicated, multi-step process and must be followed by in vitro and in vivo screening. Pharmacokinetic characteristics of potential peptides are