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REVIEW ON POLYPEPTIDE AS POTENTIAL DRUG CARRIER FOR THERAPEUTIC PURPOSE

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ABSTRACT

Peptides of natural and synthetic sources are compounds operating in a wide range of biological interactions. They play a key role in biotechnological applications as both therapeutic and diagnostic tools. While the peptide and protein therapeutic market has developed significantly in the past decades, delivery has limited their use. Although oral delivery is preferred, most are currently delivered intravenously or subcutaneously due to degradation and limited absorption in the gastrointestinal tract. Therefore, absorption enhancers, enzyme inhibitors, carrier systems and stability enhancers are being studied to facilitate oral peptide delivery. They are easily synthesized thanks to solid-phase peptide devices where the amino acid sequence can be exactly selected at molecular levels, by tuning the basic units. Recently, peptides achieved resounding success in drug delivery and in nanomedicine smart applications. These applications are the most significant challenge of recent decades: they can selectively deliver drugs to only pathological tissues whilst saving the other districts of the body. This specific feature allows a reduction in the drug side effects and increases the drug efficacy. In this context, peptide-based aggregates present many advantages, including biocompatibility, high drug loading capacities, chemical diversity, specific targeting, and stimuli responsive drug delivery. A dual behavior is observed: on the one hand they can fulfill a structural and bioactive role. In this review, we focus on the design and the characterization of drug delivery systems using peptide-based carriers; moreover, we will also highlight the peptide ability to self-assemble and to actively address nanosystems toward specific targets. Additionally, transdermal peptide delivery avoids the issues of the gastrointestinal tract, but also faces absorption limitations. Due to proteases, opsonization and agglutination, free peptides are not systemically stable without modifications. This review discusses oral and transdermal peptide drug delivery, focusing on barriers and solutions to absorption and stability issues. Methods to increase systemic stability and site-specific delivery are also discussed.

KEYWORDS: Peptide, Drug delivery, Peptide self-assembling carriers, Active targeting receptors.

INTRODUCTION

Peptides and proteins have great potential as therapeutics. Currently, the market for peptide and protein drugs is estimated to be greater than US$40 billion/year, or 10% of the pharmaceutical market. This market is growing much faster than that of small molecules, and will make up an even larger proportion of the market in the future. At present there are over 100 approved peptide-based therapeutics on the market, with the majority being smaller than 20 amino acids. Compared with the typical small-molecule drugs that currently make up the majority of the pharmaceutical market, peptides and proteins can be highly selective as they have multiple points of contact with their target. Increased selectivity may also result in decreased side effects and toxicity. Peptides can be designed to target a broad range of molecules, giving them almost limitless possibilities in fields such as oncology, immunology, infectious disease and endocrinology. For an overview of some popular therapeutic peptides/proteins. Peptide drug development has made great progress in the last decade thanks to new production, modification, and analytic technologies. Peptides have been produced and modified using both chemical and biological methods, together with novel design and delivery strategies, which have helped to overcome the inherent drawbacks of peptides and have allowed the continued advancement of this field. A wide variety of natural and modified peptides have been obtained and studied, covering multiple therapeutic areas. This review summarizes the efforts and achievements in peptide drug discovery, production, and modification, and their current applications. We also discuss the value and challenges associated with future developments in therapeutic peptides. Therapeutic peptides are a unique class of pharmaceutical agents composed of a series of well-ordered amino acids, usually with molecular weights of 500-5000 Da1. Research into therapeutic peptides started with

fundamental studies of natural human hormones, including insulin, oxytocin, vasopressin, and gonadotropin-releasing hormone (GnRH), and their specific physiological activities in the human body. Since the synthesis of the first therapeutic peptide, insulin, in 1921, remarkable achievements have been made resulting in the approval of more than 80 peptide drugs worldwide. The development of peptide drugs has thus become one of the hottest topics in pharmaceutical research.

The first half of the 20th century witnessed the discovery of several life-saving bioactive peptides, such as insulin and adrenocorticotrophic hormone, which were initially studied and isolated from natural sources. The discovery and development of insulin, a peptide with 51 amino acids, has been considered as one of the monumental scientific achievements in drug discovery. It was first isolated by Frederick Banting in 1921 and further developed by Frederick and Charles Best, and was already available for patients with diabetes mellitus just a year after its first isolation. In 1923, insulin became the first commercial peptide drug and has since benefited thousands of diabetes patients to date. However, the production of human insulin during the 20th century could not keep up with the high market demand, and animal-derived insulins, such as bovine and porcine insulin, dominated the insulin market for almost 90 years until they were replaced by recombinant insulin. More peptide hormones and their receptors with therapeutic potential were identified and characterized from the 1950s to the 1990s. Meanwhile, the technologies used for protein purification and synthesis, structure elucidation, and sequencing made substantial progress, thus accelerate the development of peptide drugs, leading to nearly 40 peptide drugs being approved worldwide. Notably, synthetic peptides such as synthetic oxytocin, synthetic vasopressin, and recombinant human insulin began to be developed in addition to natural peptides. Peptide drug development entered a new era with the advent of the 21st century, since when advances in structural biology, recombinant biologics, and new synthetic and analytic technologies have significantly accelerated the process. A sophisticated system of peptide drug development has been established, including peptide drug discovery, drug design, peptide synthesis, structural modification, and activity evaluation. A total of 33 non-insulin peptide drugs have been approved worldwide since 2000. In addition, these peptide drugs are no longer simply hormone mimics or composed simply of natural amino acids. For example, enfuvirtide is a 36-amino acid biomimetic peptide mimicking human immunodeficiency virus (HIV) proteins used in combination therapy for the treatment of HIV-; ziconotide is a neurotoxic peptide derived from the cone snail *Conus magus*, which was approved in 2004 and is used to manage severe chronic pain; teduglutide is a glucagon-like peptide 2 (GLP-2) analogue used to treat short bowel syndrome, and is manufactured using a strain of *Escherichia coli* modified by recombinant DNA technology; and liraglutide is a chemically synthesized analogue of human glucagon-like peptide 1(GLP-1), made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on lysine residue (position 26 in the sequence), which acts as a GLP-1 receptor agonist to manage type 2 diabetes mellitus (T2DM). All these peptide drugs have been used in a wide range of therapeutic areas, such as urology, respiratory, pain, oncology, metabolic, cardiovascular, and antimicrobial applications.

Advantages and drawbacks of therapeutic peptides

Therapeutic peptides commonly act as hormones, growth factors, neurotransmitters, ion channel ligands, or anti-infective agents.[1] They bind to cell surface receptors and trigger intracellular effects with high affinity and specificity, with a similar mode of action to biologics, including therapeutic proteins and antibodies. However, compared with biologics, therapeutic peptides show less immunogenicity and have lower production cost Small molecule drugs are known to have an extended therapeutic history with inherent advantages, including low production costs and sale prices, oral administration, and good membrane penetration abilities. Both naturally extracted and chemically synthesized small molecules show competitive price advantages compared with peptides and biologics (proteins or antibodies).[2] Oral administration of small molecules has the benefits of better safety and improved patient compliance, while their small size also enables them to penetrate the cell membrane to target intracellular molecules. However, their small size also means that it is difficult for them to inhibit large surface interactions, such as protein-protein interactions (PPIs), effectively. PPIs usually occupy a contact area of 1500-3000 A^2, while small molecules only cover 300–1000 A^2 of the protein surface, due to their limited molecular size. By contrast, the unique physiochemical properties of peptide drugs, including their larger size and more flexible backbone, enable them to act as potent inhibitors of PPIs the clinical use of small molecules is also limited by their low specificity compared with peptide drugs.[3] For example, sorafenib and sunitinib are tyrosine kinase inhibitors that inhibit the tyrosine kinase domain activity of vascular endothelial growth factor (VEGF) receptors, resulting in anti-angiogenic effects that are used to treat cancer patients; however, they also target other kinase receptors such as serine/threonine kinase receptors, leading to cytotoxicity they also have developed hydrogels and transdermal drug delivery systems for peptidal drug delivery.[4] A receptor-mediated delivery system is another attractive strategy to overcome the limitation in drug absorption that enables the transcytosis of the protein across the epithelial barrier. Modification such as PEGnology is applied to various proteins and peptides of the desired protein and peptides also increases the circulating life, solubility and stability, pharmacokinetic properties, and antigenicity of protein.

Peptide drug discovery

Natural peptides/hormones in the human body

The history of peptide drug discovery started by exploiting natural hormones and peptides with well-studied physiological functions for treating diseases caused by hormone deficiencies, such as a lack of insulin required to regulate blood glucose levels in patients with T1DM or T2DM.[5] Diabetes is treated either by insulin injection or by stimulating insulin secretion-related targets such as GLP-1 receptor, to produce insulin. Searching for natural peptides and hormones or replace them by animal homologues, such as insulin, GLP-1, somatostatin, GnRH, 8-Arg-Vasopressin, and oxytocin, were the initial strategies used for peptide drug discovery and development. However, the drawbacks associated with these natural peptides aroused interest in optimizing their natural sequences, leading to a series of natural hormone-mimetic peptide drugs.[6]

Peptides mimicking hormones

GLP-1 derived peptide drugs GLP-1 is a 37-amino acid peptide that regulates insulin production and secretion, with a very short half-life in vivo. Extensive efforts have been made to modify its sequence to enhance the stability of this hormone, while maintaining its potency and pharmacological effect, leading to the development of the three top-selling anti-T2DM peptide drugs: Trulicity (dulaglutide), Victoza (liraglutide), and Ozempic (semaglutide).[7]

Peptides identified from natural products

Many bioactive peptides from bacteria, fungi, plants, and animals possess therapeutic properties, such as snake venom, which is considered as a vascular endothelial growth factor (VEGF) analogue, VEGF-F or svVEGF. They are usually disulfide-rich cyclic peptides of no more than 80 residues, which can induce cytotoxicity by targeting ion channels and other membrane-bound receptors.[8] Venom peptides from snakes and scorpions have been modified for therapeutic applications. In addition, exenatide, optimized from Gila monster venom is a GLP-1 agonist and ziconotide, a venom peptide derived from *Conus magus*, has been used to treat chronic neuropathic pain.[9]

Chemical synthesis of peptides

The chemical synthesis of peptides is well-developed, particularly solid-phase peptide synthesis (SPPS) technology developed by Merrifield in 1963. SPPS technology has since been remarkably improved in terms of its methodology and synthetic materials and plays a crucial role in modern peptide production. It facilitates peptide synthesis by combining amino acid coupling and deprotection in one simple reactor, which has further led to the invention of automatic peptide synthesizers.[10] Compared with recombinant technology, the crude peptides obtained by SPPS are more monotonous, without other biological compounds such as enzymes, DNA and RNA fragments, non-related proteins, and peptides. Moreover, the impurities in the final SPPS product are easily identified because they are mainly derived from incomplete or side reactions during the synthesis procedure, making subsequent purification relatively uncomplicated.[11] SPPS consists of a cycle of coupling the carboxylic group of amino acids to a solid polymeric resin, and liberation of the amine group from the protection group. Various resins, such as 4-methylbenzhydrylamine (HMBA) resin, Wang resin, 2-chlorotrityl chloride (CTC) resin, and Merrifield resin, are used to introduce either amide or free carboxylic groups into the C-terminal of peptide. The modern peptide industry has developed various functional resins by coupling the resins with different linkers, enabling the synthesis of long peptides and peptide cyclization in the solid phase. During synthesis, the amine group of the amino acids and the side chains are usually protected by different chemical groups, which cause peptide aggregation and reduce the purity of the crude peptides. Two major SPPS strategies: Fmoc-SPPS and Boc-SPPS have been developed to remove the predominant amine protection groups, fluorenylmethyloxycarbonyl (Fmoc) and t-butyloxycarbonyl (Boc), respectively.[12]

Chemical modification of peptide and peptidomimetics

As a particular class of therapeutic agents, the biological activity of peptides is intimately related to their chemical structure. Following the synthesis of peptides, they need to be modified using medicinal chemistry techniques to mimic, stabilize, or construct an ideal secondary structure to improve their biological activity and achieve selectivity, stability, and solubility of the peptide drugs. Before modification of the lead peptide drug candidate, it is necessary to identify the minimum active sequence with the desired biological properties.[13] Classical sequence scanning, termed alanine-scan, is then commonly used to replace each residue with alanine to produce a series of lead peptide analogues to determine which key residues confer the biological activity of the lead peptide: a decrease in activity suggests that the replaced residue was important, whereas a non-significant reduction of activity suggests that the replaced residue was redundant. Further modifications of the replaceable residues and C- and N-termini of the lead peptide are then carried out to produce the final peptide drug.

Macroscopic devices for drug delivery

Nowadays, even in cases where the patient suffers localized disease or pain (of a single organ or part of it), the treatments that are usually available to physicians involve systemic drug administration. This kind of administration is particularly suitable for acute treatments as it requires minimal expertise, although it also presents several disadvantages for long-term therapies, especially the fact that the drugs administered are distributed throughout body, including the site of action.[14]

Nanoparticle-based devices for drug delivery

The challenge of delivering the correct concentration of a therapeutic agent at its site of action, and for sufficient time to be efficient, can be overcome by using traditional drug-loaded depots when the damage has well-localized targets.[15] Unfortunately, many important diseases cannot be treated with a local single application that provides a prolonged and confined drug delivery. This is the case, for example, when the simultaneous treatment of different organs is required, and this is.

Drug–ELR conjugates for drug delivery

A large number of studies have attempted to improve the bioavailability and pharmacokinetics of small-molecule drugs by conjugation thereof to ELRs, with a reduction in the therapeutic dose and an increased drug efficiency being the expected benefits of such an approach.[16] ELRs show certain intrinsic advantages for this purpose, one of which is their biodegradability as they degrade into natural amino acids, thus allowing the use of high MW ELRs, even above the renal clearance limit.

Cell penetrating peptide (CPPS) and smart sequences

Cell penetrating peptides (CPPs) are a large class containing more than 1700 different experimentally-validated sequences most common CPPs are cationic and they are widely used. A class of CPPs is derived from the α-helical domain of the Tat protein, covering residues from 48 to 60. Those residues are mainly composed of basic amino acids, such asthe TAT dodecapeptide: GRKKRRQRRRPQ The CPP role as a nanovector has been described in many reviews.[17] Despite high cellular uptake efficiency, CPPs lack cancer cell specificity. To overcome this drawback stimuli-responsive CPPs have been developed recently to enhance the cellular uptake of therapeutic cargo only in the tumor tissue. As previously reported, these stimuli can respond to pH variation or to enzyme activity or to oxidative stress. CPPs can be considered as responsive molecules when containing residues able to vary the net charge depending on the pH. One residue able to tune the net charge of the peptide is His. Therefore, Zhang et al. designed an α-helical CPP to obtain a pH-responsive peptide, by replacing all its lysines with histidines (THAGYLLGHINLHHLAHL (Aib)HHIL).[18] This peptide (TH) showed a neutral charge at physiological pH, but the net charge became positive under acidic conditions, so that its cell penetration capacity was activated.

Peptide able to interact with over expressed receptors

In certain PAs, the receptor-targeting peptides are able to induce high levels of internalization within tumor cells due to a receptor-mediated endocytosis mechanism. The peptide sequence can be composed in this manner.[19] These strategies could allow the intracellular delivery of the payload. Some known endogenous proteins are able to bind the target receptor with high affinity. A significant topic of research is about how to preserve the affinity for the over expressed receptors, especially after the conjugation to the hydrophobic moiety. Furthermore, evidence showed how all the residues which are involved in the receptor binding are well-exposed on the nanostructure surface.[20,21] Those residues maintained a conformation suitable to the interaction with the receptor.

Peptide target for integrin receptors

Integrins are heterodimers transmembrane receptors related to the cell-extracellular matrix (ECM) adhesion. Upon ligand binding, integrins activate cellular signals such as regulation of the cell cycle, organization of the intracellular cytoskeleton, and movement of new receptors to the cell membrane.[21] Integrins are one of the most important receptors that can be used in active targeting strategies. Among the different subfamilies of these heterodimeric transmembrane proteins, integrins $\alpha_V\beta3$ and $\alpha_V\beta5$ have prominent roles in angiogenesis and metastatic disseminations. The integrin αvβ3 plays a very domineering role in angiogenesis and is overexpressed in endothelial cells of the tumour. Recently a large exploration in the field of αvβ3 integrin-mediated bioactive targeting for cancer treatment has been reported. All designed peptide sequences contain the RGD motif. In most of the cases, the cyclization is commonly employed to improve the binding properties, conferring rigidity to the structure. In linear peptides, the fourth amino acid alters the binding specificity and the nature of residues, by flanking the RGD sequence.[21] The fourth amino acid could influence receptor affinity, receptor selectivity, and other biological properties.

GPR target peptide

A wide number of nanostructures were functionalized with peptides able to recognize GPCRs, in particular to target receptors for somatostatin (SST), cholecystokinin (CCK), gastrin-releasing peptides (GRP/Bombesin), lutein, and neurotensin.[22]

Bombesin receptors

The four receptor subtypes which are associated with the Bombesin-like peptides (BLP) family have been identified and found to be overexpressed in prostate, breast, small cell lung, ovarian, and gastrointestinal stromal tumors . A peptide able to bind these receptors is the bombesin (BN), which is constituted by fourteen aminoacid residues. Its eight-residue *C*-terminal peptide sequence, and many other BN analogs have been modified to selectively carry diagnostic or therapeutic agents to their receptors. They act both as agonists or antagonists. Many studies demonstrate that the.[7-14] BN fragment and its analogues conjugated on the N-terminus with amino acid linkers, aliphatic or hydrophilic moiety, they all keep the affinity for receptors.[23]

CCK receptors

In neuroendocrine origin tumors, such as medullary thyroid cancers, it was found that both CCK1 and CCK2 receptors were overexpressed. The same phenomenon was found in small cell lung cancers and in gastroenteropancreatic (GEP) tumors. The peptide CCK8

is able to recognize both receptors. However, the peptide availability on surface aggregates is not an exclusive requirement for the receptor binding: the correct peptide conformation is crucial to assure high affinity and selectivity in ligand/protein binding processes. In this case, the CCK8 peptide needs to adopt a pseudo-α-helix conformation to give high binding affinity towards to the CCK1-R and CCK2-R receptors, according to the membrane-bound pathway theory. The authors demonstrated that only peptide amphiphiles having an initial random coil conformation were able to adopt the pseudo-α-helix conformation in the presence of the receptor [24]. Unlike them, peptides like $(C18)_2$-L5CCK8, in which the peptide displays a β−sheet conformation, do not show in vitro cellular binding. Closing that chemical modification on the CCK8, the *N*-terminus seems to play an important role in stabilizing the peptide active conformation in self-assembling.

Supramolecular system based on disordered linear peptides

The design of supramolecular systems could drive the disordered peptides to fold into a stable structure. This structural modification could be a promising route to develop a new class of bio-molecules for processes in which a specific conformational rearrangement is required.[25] These considerations deserve an in-depth study of the intrinsic disorder of peptide behavior in solution and their performance on surface of nanostructures. Recently, the authors have studied the structural preferences of linear synthetic peptides with CPC-containing sequences (chemokine receptor CXCR4) characterized by the presence of some unordered amino acids.

CONCLUSIONS

As discussed in the previous sections, the future perspectives for the use of ELRs and macromolecular peptide systems mostly based on ELRs are remarkable. Thus, recombinant materials, especially those based on ELRs, show a substantial set of properties that are rarely, if ever, found together in any other class of materials currently used, or even explored, for drug-delivery applications. Peptides have become a unique class of therapeutic agents in recent years as a result of their distinct biochemical characteristics and therapeutic potential. Although peptides outperform small molecules and large biologics in some aspects, they often suffer from membrane impermeability and poor stability in vivo, due to the intrinsic limitations of amino acids. Extensive research has been carried out in terms of the discovery, production, and optimization of peptide drugs, in order to overcome these drawbacks. The integration of traditional lead peptide discovery methods with novel technologies, such as rational design and phage display, provides a reliable approach for the development of effective and selective lead peptides in a short period of time. The single or combined use of chemical and biological recombination synthetic approaches allows the efficient and reliable production of synthetic peptides on large scales. These peptides can be further modified in a site-specific manner through chemical synthesis or genetic code expansion to enhance their stability and physiological activity. Although the field of therapeutic peptides started with natural hormones, the discovery and development trends have since shifted from simply mimicking natural hormones or peptides derived from nature to the rational design of peptides with desirable biochemical and physiological activities. Major breakthroughs in molecular biology, peptide chemistry and peptide delivery technologies have allowed significant progress in the fields of peptide drug discovery, peptide production, and their therapeutic applications. More than 80 therapeutic peptides have reached the global market to date, and hundreds of peptides are undergoing preclinical studies and clinical development. These peptide drugs have been applied to a wide range of diseases, such as diabetes mellitus, cardiovascular diseases, gastrointestinal diseases, cancer, infectious diseases, and vaccine development. Considering their huge therapeutic potentials, market prospects, and economic values, we expect therapeutic peptides to continue to attract investment and research efforts and to achieve long-term success.

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