

Chemical Modification of Bioactive Peptides and Their Advances in Drug Innovation

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Abstract. Peptides are an important class of molecules in contemporary drug research. They show very high binding specificity toward biological targets. They also participate in many essential biological processes. At the same time, natural peptides encounter major difficulties in medical applications. They often display poor chemical and biological stability. They usually have a very short half-life in circulation. They are also absorbed poorly when taken orally. These limitations restrict their direct clinical value as medicines. This study focuses on the chemical modification of bioactive peptides. Several common strategies are widely investigated. Cyclization of the peptide backbone produces a more rigid and stable structure. Lipidation of the peptide chain allows longer retention in the bloodstream and strengthens interactions with cell membranes. PEGylation and glycosylation both increase hydrophilicity and reduce rapid clearance from the body. Substitution of natural amino acids with D-amino acids improves resistance to enzymatic degradation and extends biological activity. Other methods also provide important support. Solid-phase peptide synthesis offers a practical and efficient route for preparing modified peptides on a large scale. Nanocarrier systems can protect peptide drugs during administration and assist in targeted delivery. In addition, artificial intelligence is being applied to predict structural features and to design new peptide molecules with higher efficiency.

1 Introduction

Peptides are short chains made of amino acids. They play important roles in the human body. For example, they help regulate hormones, control metabolism, and send signals between cells. Because they have high specificity and usually good safety, peptides become very promising for drug development. Compared with small molecules, peptides can target large and flat protein surfaces that are difficult for other drugs to reach. This makes them effective in treating complex diseases such as cancer, metabolic disorders, and infections [1]. However, natural peptides also have many disadvantages. For example, they are easily broken down by digestive enzymes; they have short half-lives, and they are hard to take orally. These problems make natural peptides hard to use directly as medicines [2].

In recent decades, researchers have tried various chemical ways to fix these problems. Cyclization makes peptides more rigid and helps them resist enzymes. Cyclosporine and octreotide are two well-known examples [3,4]. Lipidation has also received much attention. By attaching a fatty acid chain to peptides, they can bind to albumin and stay longer in the blood. Liraglutide, a diabetes drug, is one example. In addition, PEGylation and glycosylation are used to enhance solubility, increase molecular size, and avoid rapid clearance; D-amino acid substitution helps protect peptides from protease attack. In China, peptide drug research has grown fast in recent years. Multiple studies

focus on antitumor peptides, antimicrobial peptides, and drugs for metabolic diseases. Internationally, many groups are combining modification with delivery systems such as nanoparticles and liposomes. Artificial intelligence is also used to design new peptides more quickly. These studies together show that peptide drugs are stepping onto a new stage of fast development.

Even though with significant progress, challenges still remain. One modification cannot solve all problems at once. For example, a peptide may be stable in the body, but it often lacks targeting. Or it may last longer but still have poor absorption. To address this, scientists are now testing combinations of modifications. They also use nanocarriers to improve delivery. AI models are another tool to predict which modifications will work best.

The motivation of this paper is to review chemical modification strategies for peptides and to analyze their roles in drug innovation. It will discuss the main strategies and examples. The framework of the paper is organized as follows. Section 2 discusses the limitations of natural peptides and the necessity of modification. Section 3 introduces several major modification strategies, their mechanisms, and representative examples. Section 4 explores future directions, such as the combination of multiple modifications, the use of AI in peptide design, and the role of new delivery systems. Finally, the conclusion part emphasizes the potential of modified peptides in innovative drug development.

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2 Limitations of natural peptide drugs and the necessity of modification

Peptide molecules have shown great potential in drug development due to their high specificity and targeting ability, but the inherent defects of natural peptides severely limit their clinical applications. From a pharmacokinetic perspective, natural bioactive peptides generally face problems such as low oral bioavailability, susceptibility to enzymatic degradation, poor membrane permeability, and insufficient targeting: they cannot tolerate the destruction of gastric acid and digestive enzymes, are easily broken down by proteases, and are difficult to penetrate cell membranes, resulting in extremely low efficiency in reaching target tissues; Meanwhile, non-specific distribution may cause side effects, and the duration of activity is shortened due to rapid clearance [1,2]. These defects directly lead to the failure of many natural peptides in clinical trials - for example, some natural peptides cannot be converted into drugs due to poor in vivo stability and rapid loss of activity; Even when entering clinical practice, patient compliance is often reduced due to frequent injection administration, and the high cost caused by complex production processes further restricts its application [1,2].

In sharp contrast, chemically modified peptide drugs have achieved significant success in clinical practice, confirming the effectiveness of modification strategies. For example, cyclosporine (a cyclic peptide) modified by cyclization has become a key immunosuppressant in organ transplantation, enhancing stability through a rigid cyclic structure and effectively preventing rejection reactions [3]. Another cyclic peptide, octreotide, overcomes the instability and short half-life of natural somatostatin through cyclization modification, and has been successfully used for the treatment of hormone-related diseases such as acromegaly [4]. In the field of lipid modification, daptomycin, as a lipopeptide antibiotic, has a lipid chain that allows it to directly insert into bacterial membranes and exert bactericidal effects, becoming an important weapon against multidrug-resistant bacteria [5]. However, the GLP-1 analog, liraglutide, can significantly prolong the half-life by combining with albumin through lipid modification, reducing the frequency of administration to patients with type 2 diabetes from multiple times a day to once [6]. These cases clearly demonstrate that chemical modification is the core means to address natural peptide defects and enhance their medicinal value.

3 Chemical Modification Strategies

3.1 General Principles of Peptide Modification

Although natural peptides can bind to targets in vivo with high specificity, their application is hindered by issues such as enzymatic hydrolysis, short blood retention time, and poor oral absorption. The core goal of chemical modification is to address these issues in a targeted manner by enhancing metabolic stability to

resist enzyme degradation, improving bioavailability and targeting to ensure that drugs remain in the body for sufficient time and accurately reach target tissues, while reducing off-target effects and minimizing side effects. In short, modification transforms peptides from "fragile natural molecules" into "stable and controllable therapeutic drugs" by optimizing their physicochemical properties and biological behavior.

3.2 Modification Techniques and Typical Applications

Cyclic modification can significantly enhance the rigidity of peptides by connecting the ends of peptide chains, amino acid side groups, or forming disulfide bonds (such as between cysteine residues) to construct circular structures. This rigidity not only reduces the probability of enzyme degradation but also improves the compatibility with target receptors and enhances binding specificity. For example, cyclosporine A maintains a stable conformation through cyclization, enabling it to efficiently target and bind to the calcineurin protein in immunosuppression. Octreotide, through cyclization modification, extends the half-life of natural somatostatin from minutes to hours, while retaining high affinity for somatostatin receptors. However, cyclization may reduce the water solubility of some peptides, which needs to be balanced with other modifications such as glycosylation [7]. Lipid modification can improve the interaction between peptides and cell membranes by connecting fatty acid chains, and promote their binding with albumin in the blood, thereby prolonging circulation time and enhancing therapeutic efficacy. The lipid chain of liraglutide allows it to reversibly bind with albumin, with a half-life extended to 13 hours, significantly reducing the frequency of administration. The lipid tail of daptomycin allows it to insert into bacterial cell membranes, forming channels that lead to bacterial death. This membrane targeting mechanism is key to its ability to combat drug-resistant bacteria. However, lipidation may increase the hydrophobicity of peptides, and it is necessary to optimize the length of lipid chains and connection sites to avoid aggregation [8]. In addition, PEGylation increases the molecular weight of peptides by connecting polyethylene glycol chains, reduces renal clearance, and lowers the probability of enzyme recognition. For example, PEGylated interferon can extend its half-life to once weekly administration [9]. Glycosylation can enhance the solubility and stability of peptides by adding glycosylation. For example, glycosylation modification of erythropoietin (EPO) is the key to maintaining its in vivo activity [10]. D-amino acid substitution replaces natural L-amino acids with D-type, which can resist protease degradation. For example, some antimicrobial peptides significantly improve their tolerance to intestinal enzymes through D-amino acid substitution [11].

3.3 Comparison of Cyclization and Lipidation Mechanisms

Cyclization and lipidation optimize the properties of peptides through different mechanisms and are complementary. The core of cyclization is structural rigidity, which limits the flexible conformation of peptide chains and reduces the "recognizable sites" required for enzyme degradation. At the same time, by fixing the dominant conformation that binds to the receptor, targeting is improved. The binding affinity between octreotide and somatostatin receptors is stronger than that of natural somatostatin, thanks to the conformational stability after cyclization [7]. The core of lipidation is to enhance membrane interactions and cycling persistence. The hydrophobicity of lipid chains allows them to embed into cell membranes or bind to hydrophobic regions of albumin, such as the antibacterial mechanism of daptomycin and the long-acting principle of liraglutide. In addition, lipidation may also endow peptides with new biological functions, such as transmembrane delivery ability [8]. The combination of two strategies, such as cyclic lipopeptides, can further optimize performance. For example, some antibacterial cyclic lipopeptides maintain stability through cyclization and enhance bacterial membrane penetration through lipid chains, exhibiting better bactericidal effects than single modifications.

3.4 Collaboration between synthesis technology and the delivery system

Solid-phase peptide synthesis (SPPS) is the core technology for the preparation of modified peptides. Its characteristic of gradually assembling peptide chains on a solid-phase carrier facilitates the precise introduction of cyclization, lipidation and other modifications, laying the foundation for the large-scale production of drugs such as cyclosporine and liraglutide. Enzyme-assisted modifications, such as sorting enzyme-mediated cyclization or lipidation, have become an important supplement to complex modifications due to their mild conditions and high specificity [12]. Even after modification, the *in vivo* delivery of peptides still faces challenges, such as poor oral absorption and insufficient targeting. Nanoparticles, liposomes, and other carrier systems can encapsulate peptide drugs to protect them from degradation and enhance targeting. For example, pH-sensitive nanoparticles loaded with cyclic peptides can release drugs in acidic tumor environments, reducing their impact on normal tissues; Oral peptide preparations are often encapsulated in liposomes to resist intestinal enzyme damage, and combined with absorption enhancers to enhance bioavailability [13]. The combination of modification strategies and delivery technologies has greatly expanded the application scenarios of peptide drugs.

4 Future prospects and innovation directions

4.1 Research significance

As an intermediate state between small molecule drugs and biologics, chemically modified peptides possess both the ease of synthesis of small molecules and the high specificity of biologics. Its molecular weight is between the two, which not only avoids the off-target risk of small molecules, but also makes it easier to produce and more cost-effective than biological agents such as antibodies. For example, cyclic peptides typically have a molecular weight of 500-2000 Da and can target "flat" protein surfaces that are difficult for traditional small molecules to bind to. The stability of the modified peptide makes it easier to exert its effects through oral or local administration than antibodies. This unique advantage makes it an irreplaceable application potential in fields such as tumors, infections, metabolic diseases, etc.

4.2 Future direction

The combination of multiple modification strategies, such as cyclization, lipidation, glycosylation, etc., can compensate for the shortcomings of a single modification. For example, the hybrid peptide of "cyclization+lipidation" can maintain structural stability through cyclization and enhance membrane penetration through lipid chains, demonstrating potential in intracellular targeted drugs such as nuclear receptor agonists. PEGylation+D-amino acid substitution can simultaneously prolong half-life and enzyme tolerance, making it suitable for the field of long-term treatment. Artificial intelligence (AI) assisted design utilizes AI to predict peptide modification sites (such as optimal cyclization position, lipid chain connection efficiency), conformational stability, and binding energy with targets, which can significantly shorten the research and development cycle. For example, AI models have successfully designed cyclic lipopeptides with high antibacterial activity by analyzing massive peptide target binding data, which outperforms molecules screened by traditional trial and error methods [14]. Upgrade and develop responsive carriers for intelligent delivery systems, such as pH, enzyme, and temperature-sensitive nanoparticles, to achieve precise release of peptide drugs in target tissues. For example, liposomes responsive to the tumor microenvironment can specifically deliver modified peptides to solid tumors, reducing systemic toxicity. The combination of an oral drug delivery system and intestinal mucosal targeted peptide modification can further enhance the intestinal absorption efficiency of peptides.

4.3 Policy and Industry Suggestions

The relevant parts need to optimize the regulatory pathway for the unique properties of modified peptides (such as physicochemical characteristics between small molecules and biologics). Regulatory agencies can develop specialized review guidelines, clarify their quality control standards, clinical trial design points (such as immunogenicity evaluation), and accelerate the transition from laboratory to clinical. At the same time,

it is necessary to strengthen the collaboration between industry, academia, and research to establish a shared peptide modification technology platform (such as high-throughput modification screening and large-scale synthesis facilities), promote the combination of basic research in academia (such as the discovery of new modifying enzymes) with the industrialization capabilities of enterprises (such as low-cost SPPS processes), and lower the innovation threshold. Breakthrough production bottlenecks and develop automated solid-phase synthesis equipment and continuous flow purification technology to reduce the production cost of modified peptides [15]. The ultimate goal is to explore green chemistry methods (such as enzymatic substitution for chemical synthesis), reduce the use of organic solvents in the synthesis process, and enhance industrial sustainability.

5 Conclusion

This paper discusses how chemical modification can transform fragile natural peptides into stable and effective therapeutic drugs. Overall, the main finding is that different strategies can solve different problems: Cyclization makes peptides more stable and helps them bind targets better. Lipidation lengthens circulation and enhances interaction with the membrane. PEGylation and glycosylation increase solubility, reduce rapid clearance, and maintain biological activity. D-amino acid substitution provides resistance to enzymatic degradation. In addition, Solid-phase synthesis and nanocarrier systems also give new options for delivery. New studies also show that combining different strategies and applying AI-assisted design can create stronger and safer peptide drugs. This work shows that chemical modification is not only a technical trick but also a key step to turn fragile peptides into useful medicines. Modified peptides can act as “middle drugs” between small molecules and biologics. They have unique advantages in treating cancer, infections, and metabolic diseases. Nevertheless, this research still has certain limitations. First, no single modification strategy can fix all of the problems, such as bioavailability and targeting. Second, some modifications may increase hydrophobicity and cause aggregation and raise concerns about immune reaction. Furthermore, large-scale production is still costly and requires advances in technology, such as automated synthesis. Looking forward, future studies should pay more attention to integrating multiple modification techniques in a rational design framework, supported by AI and computational modeling to predict optimal strategies. In parallel, the development of responsive delivery systems, such as pH-sensitive or enzyme-triggered nanoparticles, will help achieve precise drug release. Greater collaboration between academia, industry, and regulatory agencies will also be essential to accelerate translation from laboratory to clinic. In conclusion, chemical modification of bioactive peptides represents a promising and dynamic field that continues to evolve. With continuous innovations, peptide therapeutics are

expected to play an increasingly important role in the next-generation drug development.

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