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REVIEWS

Peptide drugs application in metabolic diseases and discovery strategies

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[Abstract] Peptides (or polypeptides) are generally defined as those molecules compounded with less than 100 amino acids linked by peptide bonds, and the relative molecular weight is less than 10 000 Da usually. To date, more than 7 000 naturally peptides have been identified, and they play critical roles in mammalian pathophysiology. Peptide drugs are a unique kind of pharmaceutical compounds due to their different biochemical and therapeutic characteristics. This review will briefly introduce the application of peptide drugs in the treatment of common metabolic diseases and available discovery strategies for potential peptide drugs.

[Key words] Peptides drugs; Metabolic diseases; Discovery strategies; GPCRs

1 Introduction

Peptide therapeutics are used for a range of disorders, such as diabetes, cardiovascular disease, osteoporosis, central nervous system disease, and cancers among others[1]. Compared with small molecule drugs, peptide drugs have advantages including high biological activity, strong specificity, weak toxicity, less interaction with other drugs, and excellent affinity with their receptors[2]. The most attractive merit of peptides over small molecule drugs is their low systemic toxicity, because most of them were derived directly or indirectly naturally, and after degradation only amino acids left[3]. Compared with protein and antibody drugs, peptides drugs have other advantages such as lower production cost, higher activity per unit mass, higher stability[4], and less immunogenicity, these even for the artificial peptides[5]. Together with the maturation of peptide synthetic technology, acceptable prices, recognized by the market, in recent two decades, peptide drug development has obtained more and more attentions, although their limitations like short circulation time, low oral bioavailability, and low plasma stability and so on are still there.

In general, peptides work as signaling molecules to bind with specific cell surface receptors, the core of many intracellular physiological actions[6-7]. G protein-coupled receptors (GPCRs) are the main targets of the marketed peptide drugs, thereinto, receptors for Glucagon-like peptide-1 (GLP-1),

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GLP-2, chemokine 4, opioid, growth hormone, melanocortin, and oxytocin are famous examples[8]. In addition, the targets of peptide include cytokine receptor superfamily and natriuretic peptide receptor family[8]. The number of peptide drug targeted receptor molecules is increasing continuously.

Peptide drug approvals have grown steadily over the past 60 years and accounted for about 5% of the global pharmaceutical market in 2019, with sales exceeded 50 billion USD[9]. The global peptide market is growing at an average rate about 7.7% and continually growing and expanding[9-10]. By 2021, there are 88 peptide drugs have been approved by the U.S. Food and Drug Administration (FDA) as we know, 10 out of them in the metabolic diseases field[7,11-14]. The FDA approved peptide drugs for metabolic diseases are listed in Table 1, account for about 12% of peptide drugs ever in the market. The peptide research related to metabolic diseases is an attractive field in pharmaceutical studies globally in both industry and academy.

2 Peptide drugs for the metabolic diseases

All life activities are dependent on metabolic homeostasis, which is maintained by multiple biological pathways in the body. Metabolic diseases are slow developing and intractable diseases induced with a group of complex etiologies with different aspects of metabolic homeostasis disruption. It's estimated that nearly 35% adults and 50% aged people have metabolic diseases in the US[15]. The prevalence of metabolic diseases among aging people in China was about 36.9% in 2019[16]. The most common metabolic diseases include obesity, diabetes, nonalcoholic fatty liver disease (NAFLD) or metabolic (dysfunction) associated fatty liver disease (MAFLD), osteoporosis, and cardiovascular

Table 1 FDA approved peptide drugs for Metabolic diseases[7,9]

Peptide name	Brand name	Indication	Derived from	Production	Administration	AA	FDA Approval Data
Pramlintide[57]	Symlin	Type 1 and 2 diabetes	Human amylin	Synthetic	Subcutaneous	31	03/2005
Exenatide[50]	Byetta	Type 2 diabetes	Gila monster Exendin- 4	Synthetic	Subcutaneous	39	04/2005
Liraglutide[19]	Victoza	Type 2 diabetes and Obesity	GLP- 1	Recombinant	Subcutaneous	37	01/2010
Albiglutide[58]	Tanzeum	Type 2 diabetes	GLP- 1 fused to Human serum albumin	Recombinant	Subcutaneous	2×30	04/2014
Dulaglutide[59]	Trulicity	Type 2 diabetes	GLP- 1 fused to IgG	Recombinant	Subcutaneous	2×30	09/2014
Lixisenatide[25]	Lyxumia	Type 2 diabetes	Gila monster Exendin- 4	Synthetic	Subcutaneous	44	07/2016
Semaglutide[21]	Ozempic	Type 2 diabetes and Obesity	GLP- 1	Recombinant	Subcutaneous, Oral	31	12/2017 09/2019
Salmon Calcitonin[60]	Miacalcin	Osteoporosis and Hypercalcemia	Salmon Calcitonin	Synthetic	Subcutaneous	32	07/1986
Teriparatide[28]	Forteo	Osteoporosis	Parathyroid hormone	Recombinant	Subcutaneous	34	11/2002
Abaloparatide[29]	Tymlos	Osteoporosis	Parathyroid hormone related peptide	Synthetic	Subcutaneous	34	04/2017

AA, amino acids; GLP- 1, Glucagon-like peptide-1; IgG, Immunoglobulin G.

diseases[17]. In recent years, several peptide drugs for metabolic diseases treatment have become blockbusters in the pharmaceutical market.

2.1 Peptides for Obesity and Type 2 diabetes mellitus(T2DM)

Saxenda and Victoza (both Liraglutide) and Rybelsus and Ozempic (both Semaglutide) are the only two drugs in obesity drug market, both are peptides. Liraglutide is an agonist for GLP-1 receptor (GLP-1R) whose physiological effects include increasing insulin release, decreasing glucagon secretion, delaying gastric emptying, and reducing sense of hunger[18]. Clinically, Victoza is used in the treatment of diabetic patients, and Saxenda used for weight loss of obese patients[18]. Studies found that adding liraglutide to a lifestyle intervention experiment resulted in an average weight loss of 4 to 6 kg in one year[19-20]. Similar as liraglutide, semaglutide also has effects both in the hypoglycemic and weight loss. Studies pointed out that compared with the placebo group, semaglutide 14 mg group lost 3.7 kg body weight in 26 weeks treatment[21-22].

GLP-1 analogs are acknowledged as the most successful peptide drugs for treatment of T2DM. The earliest GLP-1 analogs in this category are those with low amino acid sequence homology to human GLP-1, such as exenatide, lixisenatide and loxenatide, which are all based on the polypeptide Exendin-4 in saliva of American lizard[23-25]. While, the current category is with high homology to human GLP-1, obtained through the substitution or processing of a few amino acid (AA) residues in the sequences, such as semaglutide, liraglutide, benaglutide, and dulaglutide[21-23,26].

2.2 Peptides for Osteoporosis (OP)

Salmon Calcitonin, Teriparatide and Abaloparatide are marketed peptide drugs developed for OP treatment. Salmon Calcitonin is a drug approved in 1986, no longer a first-line treatment for OP clinically today. Teriparatide has unique roles and advantages in the treatment of OP fractures, can promote bone formation, increase bone density to reduce the risk of fractures[27-28]. Abaloparatide is a latest developed drug for OP, can increase the bone density of the OP patients, considered with better bioeffect than teriparatide[29].

2.3 Peptides for MAFLD/NAFLD

Drug development for MAFLD/NAFLD is currently a major direction in the pharmaceutical industry. There is no MAFLD drug in mainstream market, yet. The current peptide drug developing for the treatment of MAFLD include liraglutide, cotadutide, and semaglutide[30]. These peptide drugs approved for other disease have been found with the effect of improving liver inflammation and liver fibrosis, now all at different clinical trial stages on or after phase Ⅱ[30-33]. Among them, cotadutide is believed possessing better effect than liraglutide. Semaglutide also has been extended in the treatment of nonalcoholic steatohepatitis (NASH) in clinical trials[31-33].

Our laboratory works on metabolism diseases for years. After the discovery of Obestatin in 2005 with similar strategy[34], we have discovered a novel circulating peptide hormone named Metabolitin (MTL), a potential MAFLD drug[33]. After the identification of its endogenous receptor GPRC6A, we found MTL-GPRC6A can improve hepatosteatosis and insulin resistance, regulate the lipid absorption and intestinal hormone Neurotensin and GLP-1 secretion in intestine. More interestingly, the biological effect of oral MTL administration is consistent with that of intraperitoneal injected one. This study was published in Journal of Hepatology in February 2020, which laid the foundation for the follow-up research and introduced new bioactive molecule and signaling pathway for MAFLD diseases[35]; most importantly, it seems MTL works through a new strategy which is absent in the MAFLD treatment before.

3 Peptide drugs discovery strategies

Peptide drug is still a small class relative to other drugs. Unlike small molecule drug discovery has been highly matured to achieve comprehensive and systematic screening, peptide drugs screening strategies are still sparse and limited[6,36]. So far, there is no common and replicable development strategy for peptide in the pharmaceutical industry, but still dependent much on basic research to find potential targets for subsequent preclinical and, hopefully clinical development. Based on the properties of peptide itself, related pathways, molecule-molecule interactions and individual biofunctional characteristics, usually, laboratories develop their own specific strategies under a basically same peptide study framework (Fig. 1).

Due to the aforementioned limitations of peptide, peptide drug discovery is also a complicated and struggling field in pharmaceutical industry. So far, for the most time, only the well-studied and well-understood peptides, the so called 'low hanging fruits', may payback the effort of those studies[36]. However, once there's major breakthrough for an individual peptide candidate, peptide drugs' high efficacy, low immunogenicity, rarely observed drug-drug interactions, and nonmechanistic-based toxicology[37] will make the research and development process much smoother compare to other drug categories.

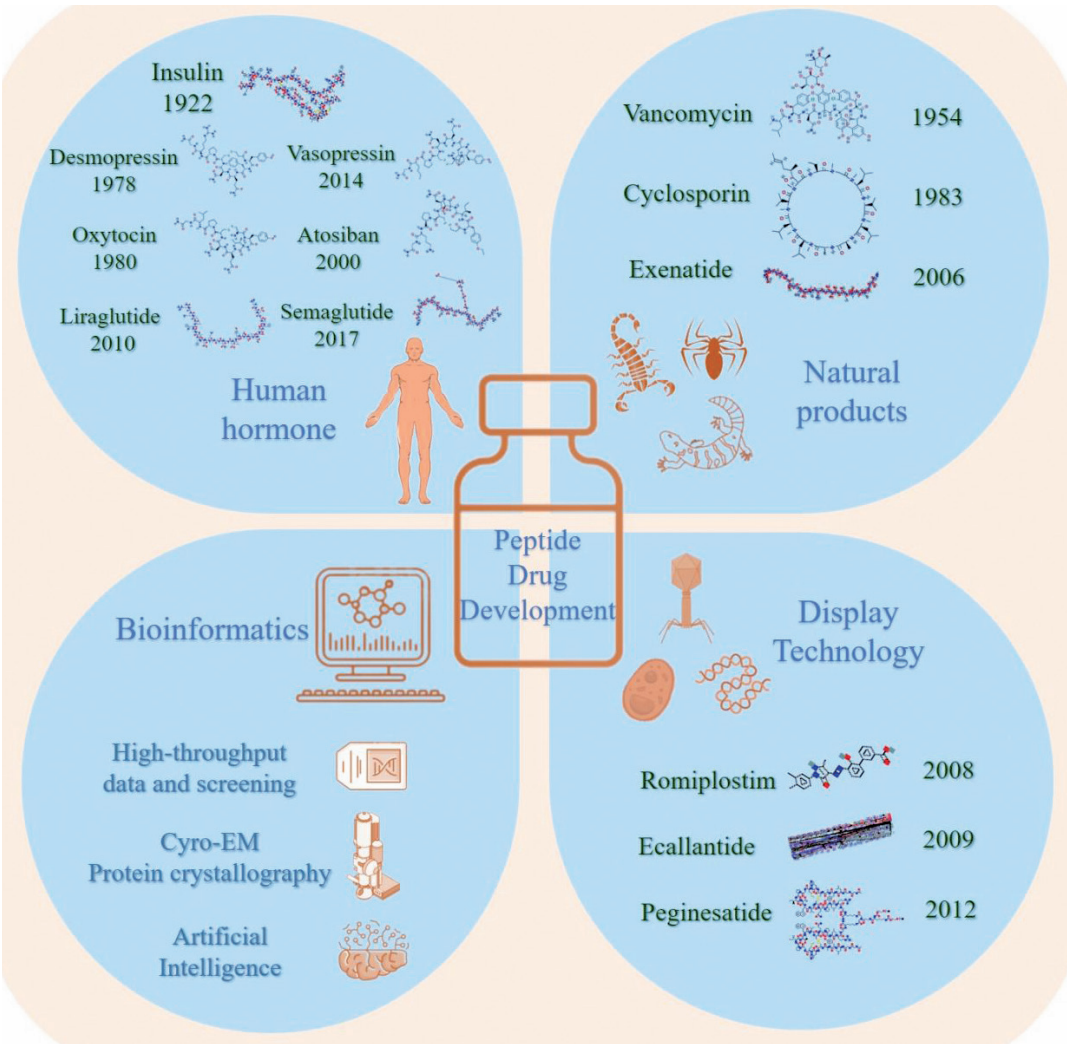

Fig.1 Peptide drug development, discovery resources and techniques.
All the molecular structure used in this figure are obtained from the PubChem website: https://pubchem.ncbi.nlm.nih.gov/.

3.1 Based on known human peptide hormones or functional peptides

Based on known human peptide hormones or known functional peptide to start drug development, is the most commonly used strategy for peptide. Started from insulin, the first major peptide drug which was identified in 1921 and commercialized in 1922, peptide researches have mainly focused on innate human peptide hormones in the last several decades[38]. Peptide hormones, as natural biological molecules, usually represent viable and validated leads for drug discovery. These endogenous molecules exercise their hormonal function through their receptors or target proteins, most of them have very short half-lives. Once a bioeffect determined peptide approach to the preclinical study stage, inevitably, the medicinal chemistry techniques are involved to improve their stability, pharmacokinetics and pharmacodynamics[39-41].

Among peptide drugs, there's a particularly successful example for this strategy, GLP-1. This 37 AA long peptide can be broken rapidly by dipeptidyl peptidase 4 (DPP4) *in vivo*, its degradation susceptibility bottlenecks its possibility to develop into a drug[42]. A replacement modification of position 2 Alanine residue by other short side-chain AAs like glycine improves the molecule's ability to against enzymes' degradation and smoothes the subsequent pharmaceutical processing. Besides, further modifications are needed to improve peptides' drug product performance. *D*-amino acids and unnatural amino acids substitution, amino-terminal (*N*-terminal) capping, deamination and particular residues replacing are common ways[43]. Since 1980s, based on this strategy, nearly 20 peptide drugs have been successfully developed, such as oxytocin, vasopressin, desmopressin and atosiban[44-45].

3.2 Based on natural product from other species

Peptides from other organisms are another resource of drug candidates. This natural source provides opportunities for novel bioactive peptides mining and drug development[46]. These peptides often have unique structures and nonstandard amino acids like ornithine, kynurenine, etc., which endows them better drug properties including higher selectivity, potency and *in vivo* stability.

The number of peptide drugs discovered from non-human species keeps increasing. Some peptide drugs, such as vancomycin and cyclosporin, are derived from bacteria and fungi, which are synthesized by large multi-modular enzymes called nonribosomal peptide synthetases but not by ribosome with nonstandard amino acids[47]. Venomous animals' vast array of peptide toxins supply variety of pharmacological targets. Most of these venoms are disulfide-rich peptides, highly permissive to mutation, which endues them good engineering operability for screening new functions[48-49]. For example, the human hormone derived GLP-1 peptide undergoes rapid *in vivo* renal clearance (1-2 minutes), but the Gila monster venom derived 39-AA residues peptide exendin 4, can be stable under the DPP4 degradation and have much slower renal clearance rate. Meantime, this 53% human GLP-1(7-37) homologous peptide has high affinity to the GLP-1 receptor, supporting its development into the drug exenatide[43,50].

3.3 Emerging strategies based on new techniques and approaches

Theoretically, thousands of untapped peptides could be served as targets for drug development. However, the traditional screening, purifying, sequencing, and then elucidating a hit is a time-consuming and inefficient approach. The involvement of some state-of-the-art techniques in drug discovery has created new and possibly powerful strategies for polypeptide drug development.

Molecular display technology has been invented for almost four decades, with the maturity of recombinant technologies and library design, in recent days, this method has become more efficient and applicable for the discovery of peptide leads

against biological targets. The first approved peptide drug by using display technology was peginesatide, an erythropoiesis-stimulating agent without homology with natural erythropoietin, screened from a peptide library[51]. There are other approved peptide drugs also based on this strategy, such as romiplostim[52] and ecallantide[53].

With the rapid development, bioinformatics and computational biology has ushered in an era of quicker, cheaper and more effective drug discovery. High-throughput data such as genomic, transcriptomic and proteomic data accelerate establishment of protein/peptide libraries and identification of drug targets. Cryo-electron microscopy (Cryo-EM) greatly accelerates the protein structural information collecting, which paves the way for more realistic protein-peptide docking information and more informative virtual screening[54]. Now, it's much efficient to obtain a predict information such as structure, surface charge or interaction affinity of generated peptide.

3.4 A glance at future peptide drug discoveries and applications

Due to the mechanisms of peptide to regulate the bioeffects, as it is being, peptide drugs developed in the following years will still be used to treat metabolic disorders. Because of the complicated modulations peptide involved in, peptide drug development is still concentrated in the preclinical development stage in the next decade. There still need new techniques to deal with the pharmaceutical disadvantages of the peptides, from upgraded screening library, synthesis of specially constructed peptides, to efficient delivery methods for the discovery, production, and optimization of successful peptide drug development. However, with the development of advanced techniques such as the protein structure prediction tool Alphafold[55], and the powerful tool just developed by Cao et al. to design protein binding proteins using only the 3-dimentional structure of the target[56], the successful rate of peptide drugs could be accelerated.

4 Conclusion

Peptide drugs have raised tremendous interest in pharmaceutical industry and in academic researchers in recent years with their outperformed characteristics over small molecules and large biologics. Compare to small molecular and macromolecular drugs, peptides have obvious advances to meet medical needs. Although the peptide drugs are still a smaller proportion in modern pharmaceutical market, with the peptide drug discovery in both academy and industry actively, there will be a promising future for this field.

5 Conflicts of interest

These authors have no conflict of interest to declare.

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