International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

Peptidesastherapeutic Agents

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Abstract: ***peptides play a vital role in human physiology. There are about 700 naturally occurring peptides. They show many good specific characters. Peptides are used in field of medicines, drugs, therapies.***

Keywords: peptides, natural occurring peptides, classification, historic reviews of peptides, applications

1. Peptides: Introduction

More than 700 naturally occurring peptides have been identified, and they play important role in human physiology, including actions like hormones, neurotransmitters, growth factors, ion channel ligands. peptides are selective and effective signalling molecules that bind a specific cell surface receptors.as they show attractive pharmacological profile and intrinsic properties, peptides represent as an excellent starting material to design a novel therapeutic drug. [1]

Peptides specificity shows good safety, tolerability and efficient profiles in humans. This aspect plays an important and differentiating factor of peptides when compared with traditional small molecules andthe production costs are lower [2]

Peptides play a vital role in production and various applications in the field of medicines, drugs, therapies and on the whole in the pharmaceutical field. The utilization of peptides as therapeutics has evolved with time and there is continues growth with change in drug development and as well as in the treatment paradigms. In first half of 20^{th} century, peptides isolated from natural sources like insulin provided life-saving medicines. [3] In the last five years(2015-2019), the US food Drug Administration(FDA) have authorized a total of 208 new drugs, among them 15 were peptides or they a peptide-containing molecule.[4]

Delivering drugs specifically to patient neoplasm is a major and ongoing clinical challenge. In addition to peptide-based natural hormone analogs, peptides have been developed as drug candidates to disrupt protein-protein interaction and target or inhibit intracellular molecules. [5]

There are many therapeutic peptides which are known for pharmacological and biological activities. With antioxidant, antimicrobial, anti-inflammatory and antihypertension properties. At present the antiviral activity of peptides is also been investigated. [6]

With this one of the most challenging tasks on the development of peptide as the therapeutic drug is to increase its oral bioavailability. Due to their high molecular weight, low intestinal permeability, hydrolysis susceptibility, high polarity peptides as drugs are supplied through injection. [7]. The need for injection made peptides less attractive and appealing for outpatient therapy and that required chronic. [8] With the advancement of peptides research, so far there are eight drugs that have been sold in the market which are orally administrated. Well known examples are linaclotide, which is used for irritable bowel syndrome with constipation and cyclosporine, used as immunosuppressant. [9]

One important point to be noticed is that naturally occurring peptides are often not convenient as therapeutic drug as they have intrinsic weakness, poor chemical and physical stability, short circulating plasma half-life. Positive part is that these weaknesses have be successfully resolved through 'traditional design' of therapeutic peptides. This method includes multifunctional and cell-penetrating peptides and peptide drug-conjugates and technologies which aims at alternative routes of administration.[10]For example, the peptide-based medicine Lupron from Abbott laboratories for the treatment of prostate cancer achieved global sales in 2011.[11]

Another important aspect is about rational peptide drug design to improve the physicochemical properties of natural peptides that shows tendency to aggregate and some are water soluble. The chemical design method is to avoid aggregation which includes the corruption of hydrophobic patches, this can be achieved by substitution or N-methylation of particular amino acids. [12] If there are solubility issues of peptide drugs, the common focus is on isoelectric point and charge distribution with relation to pH of the desired product. [13]

There is a general belief that second-generation peptide medicines optimized for therapeutic use through rational design lead to user-friendly products. For example, glucagon analog that is liquiddosage which is stable at that form is suitable for application as a ready-to-use rescue tool. The main disease areas which are aimed intherapeutic use of peptide drugs are metabolic diseases and oncology. The use of peptide therapeutics in the treatment of diabetes and obesity is widely used in North America and the marketed drug includes teduglutide, a GLP-2 receptor 2 agonist. [14]

Different methods of peptides synthesis are available and successful as well. Size and potential modification of peptides are the major determinants for choosing the synthesis method. Chemical synthesis which includes solid and solution phase peptide synthesis and recombinant expression systems and the most convenient synthetic strategies. [15]

Solution phase peptide synthesis is being widely used as it is low-priced precursors and easy to handle.it is been the method of choice in the industrial production of smaller peptides. The dipeptide sugar replacement aspartame-1-phenylalanine-methyl ester is commonly synthesized in solution phase synthesis. With this solution synthesis is applied in the production of hormone analogs, but the major disadvantage of synthetic approaches in solution phase is the limitation of the number of amino acids to be joined. This phase is time consuming and the yield are limited which depends on the coupling efficiency. [15]

On the other hand, solid phase peptide synthesis was developed by Merrifield in 1963. Peptides were designed on polystyrene resins coupled to variable linkers depending on the desired C-terminus cleavage. The growing peptide chains are covalently bonded to the solid support during the synthesis and is cleaved off using HF for the Boc-strategy and TFA in the Fmoc-strategy. It is not necessary to isolate any intermediate products in solid phase synthesis. Coupling yields are strongly increased by the possibility of applying an excess reagent in each reaction step that is filtered from the solid support during washing. At final stage after the complete synthesis, peptide is cleaved off the solid support.[16]

On more method for synthesis of peptides involves a combination of both solution and solid-phase peptide synthesis of long peptide sequence. In this method peptide fragments are synthesized on solid support up to certain length then after the cleavage from resins, the fragments are condensed yielding a longer product. The advantage of this method is that it gives high yield and purity compared to other methods. [17]

Ultimately, the cost of peptide synthesis depends on the length and composition of the peptide chain and sequencing and its yield purity. Building peptides as therapeutic compounds remains cost-intensive. Since peptides are smaller in size, they are superior to the latter, which are large in size and cause allergic effects. They show high target affinity and specificity since they naturally act in organisms in very small concentration. On the other hand, peptides accumulate in organs such as liver and kidney, but are not dangerous to undergo any unexpected reactions. They show normal metabolism and excretion. They also show interaction with other drugs in the system. Thus, it shows less problems during simultaneous application of other drug molecules. [18]

After a compound is synthesized, before being approved as a drug, there is a need for all the pharmaceuticals to undergo different types of testing, clinical phases. Phase I, checks the pharmacokinetics, pharmacodynamics and safety of a drug on few probands. Phase II checks the effectiveness of the compound for a specific disease and tested in small number of patients andeffective dosage is found. Phase III is a large-scale study of testing the effectiveness and side effects of the drug. After all these procedures the drug is submitted for approval to medicinal agencies. If the result is positive, the drug will receive approval, approved drug is further sent for phase IV to screen the short and long-term side effects of the particular compound. [19]

In the current development, there has been a good progress in the diagnosis, treatment and prevention of many types of cancer. Currently cancer treatments involve surgery, chemotherapy, radiations, biological and hormonal therapy. [20]

Pore-forming peptides target cancer cell membranes and induce cell death either by necrosis or apoptosis. In necrosis, Anti-microbial peptides target the negatively charged molecules on the cancer cell membrane and caused cell lysis. Whereas in apoptosis, they cause disruption of the mitochondrial membrane. [21] many of the antimicrobial peptides are short and have cationic charges. They form amphipathic structure in non-polar solvents. They bind to the negatively charged bacterial cell membrane through electrostatic interactions, which results in the death of prokaryotes. [22]

The second group of therapeutic peptides are cell penetration peptides (CPPs) and these peptides are 5-30 amino acids in length and can translocate through the plasma membrane and transport cargos ranging from small molecules like DNA, siRNA and plasmids to oligonucleotides and proteins and these CPPs provide a promising mechanism for drug delivery. [23] these CPPs are hydrophobic in nature and plays a vital role in the interaction and insertion of peptides into the cell membrane and they are taken up by the cell either by an energy-independent or energy-dependent process. [24, 25] recently Lim et al. designed novel CPP BR2 which is 17 AA peptide based on the CPP motif of buforin IIb. This peptide was cytotoxic against HeLa cells, HCT116 human colon cancer cells and B16-F10 mouse melanoma cells but not N1H3 T# mouse fibroblasts. [26]

The third group of peptides are the tumour-targeting peptides (TTPs), these peptides target markers such as receptors expressed on the tumour cell membrane. [27] TTP peptide NGR contains a Asn-Gly-Arg sequence, binds to aminopeptidase N which is expressed by endothelial tumour cells such as pancreatic cancer.[28] non-small cell lung carcinoma.[29] scirrhous gastric cancer.[30] another TTP peptide is RGD contains a sequence Arg-Gly-Asp and recognises as well as binds to integrin αvβ3 and αvβ5, which is expressed on the membrane of lung cancer,[31] brain tumours, [32]

For the improvement in peptide drug penetration through biological barriers can be achieved by adding modules for passive and active transport.[33] incorporation of positively charge amino acids, especially at terminal positions improves cell and tissue penetration of peptides. [34]

When compared to antibodies, these peptide drug show few drawbacks; they have no resistance to serum and tissue proteases in vivo and are rapidly cleared from the circulation in a matter of minutes. Peptides cannot access intracellular targets. Research into novel peptide drug candidates have suffered compared with new scaffold-based drug candidates. However, there have been a number of recent technological developments that promise to address the key issues of protease resistance, serum half-life and

trans-membrane delivery, and so change the landscape for novel peptide therapeutics. [35]

2. Historic Overview

With advances in DNA recombination and protein purification technology, the first isolation and commercialization of insulin with a 51 amino acid peptide in 1920s, gave a great scope to peptide drugs in pharmaceutical industry. Over the past two decades, nearly about 60 more peptide drugs have been approved worldwide. With the intended usage of these certified drugs, it appears that metabolic disorders and cancer are the predominantly targeted diseases. [36]

Peptides represent a unique and special class of pharmaceutical compounds. Advances in protein synthesis have increased the complexity of peptides being produced for therapeutic purposes.in the 1980s all the peptide drugs were under 10 amino acids long but whereas now they are up to 40 amino acids long. [37]

A global industry analysis on peptide therapeutics predicted an annual growth rate of 9.1% (2016 to 2014). The top selling peptide drugs for metabolic disease such as liraglutide and glucagon like peptide-1 both had at least two billion USD sales per annum [38]. Peptide drugs including leuprolide, gosarelin also contributed to over four billion USD in sales. [39]

There is certain increase in popularity in peptide usage due to success of first-class peptides, due to the results followed based on the research programs.

3. Application of Peptides to Therapeutics

Therapeutic use of peptides combines the selectivity and properties of peptides with their ability to pass through the cell membrane. The conjugating peptides with imaging agents and cytotoxicity allows accurate targeting of substance towards certain cells.Peptides function as antivirals, anticancer drugs, where some target HIV, flu hepatitis and even Alzheimer being licensed for therapeutic use.[40]

There are different sources and chemical nature of early peptides and here are few examples [41]

Peptides	Source	Introduction to Clinic
Insulin	Isolated from canine and bovine pancreatin	1920s
Calcitonin	Isolated from salmon ultimobranchial gland	1971
Oxytocin	Synthetic	1962
Leuprorelin	Synthetic analog of gonadorelin	1984
Vasopressin	Synthetic	1962

It is not surprising but the characteristics of peptides entering clinical development have seen remarkable evolution over time. These changes advances in peptide chemistry, purification and isolation, Improved tools for molecular pharmacology, shifting healthcare trends, and emergence of competing molecular types such as monoclonal antibodies.

- A team led by Prof GE Ruowen, Department of biological sciences, NUS has developed a cyclic peptide named BC71 which is able to supress tumour growth in murine models. BC71 peptide accumulates in cancer, attaching itself to GRP78 protein present on the surface of cancer cells as well as cancer blood vessel endothelial cells, which helps in cell death cell process. [42]
- GnRH-targeting peptides were formulated into a range of delivery formats and it was approved for prostate cancer, assisted reproduction, endometriosis and for other indications as well. This development shifted towards small molecule GnRH antagonists in the year 2000s. [43]

4. Conclusion

Peptides play a vital role in drugs production and has great scope in treating cancer. Peptides function as antivirals, anticancer drugs, where some target HIV, flu hepatitis and even Alzheimer. Thus, this article provides information about peptides and its usage in modern drug synthesis in the field of chemistry and medicine.

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