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# Glycosylation is a useful synthetic technique to increase the bioavailability of medicinal peptides

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## Introduction

Glycosylation of peptides is a promising technique for enhancing peptide medication absorption through biological membranes and altering their physicochemical properties. This review discusses several glycoconjugate synthesis methods as well as recent advances in the creation of glycosylated peptide therapies. Furthermore, the effects of glycosylation on overcoming current obstacles to peptide transport in the mouth and brain are discussed.

Peptides offer high activity, target specificity, low toxicity, and limited non-specific and drug–drug interactions, making them viable therapeutic candidates for a variety of illnesses. There have been numerous attempts to improve the pharmacological characteristics of peptide medicines and transport them efficiently to target areas, notably via non-parenteral methods. However, peptides' weak physicochemical qualities prevent them from being delivered effectively. More importantly, biological obstacles such as fluctuating pH across the Gastrointestinal Tract (GIT), the presence of proteases, and physical barriers can make oral peptide distribution difficult. The phospholipid bilayer in biological membranes, for example, prevents peptide medicines from penetrating fully into intestinal cells. In addition, insufficient absorption and quick breakdown by proteolytic enzymes are further roadblocks that contribute to the low oral bioavailability of peptides (less than 1-2%) [1].

To address these obstacles, many strategies have been investigated, which can be divided into two categories: (1) chemical peptide modification, and (2) peptide formulation (including use of absorption enhancers). Chemical techniques to improve the pharmacological profile of therapeutic peptides include glycosylation, PEGylation, lipidation, and cyclization. Chemical modifications, such as the addition of glycosyl units to peptides, can produce a variety of changes in their properties, including conformational configurations, chemical, physical, and biological properties, and functions. This article discusses the challenges that peptide medications must face, as well as the importance of glycosylation as a peptide delivery technique and its uses in the development of therapeutic peptides. It also gives information on how to make glycoconjugates synthetically.

The addition of carbohydrate moieties to peptides alters their physiological characteristics, perhaps increasing their bioavailability. Peptide glycosylation has several advantages, including: (1) targeting specific organs and improving biodistribution in tissues, (2) improving penetration through biological membranes, (3) increasing metabolic stability and lowering clearance rate, (4) receptor-binding, (5) protecting amino acid side chains from oxidation, and (6) maintaining and stabilising the physical properties of peptides, such as precipitation, aggregation, and thermal and kinetic denaturation. By targeting glucose transporters on the surface of biological membranes, sugar-peptide conjugation can also enable active transport of modified substances across cell membranes. The beneficial effect of glycosylation on the native peptides' pharmacokinetic properties leads to an improvement in their oral absorption and bioavailability. Glycosylation with N and O links N- and O-linked glycosylation, which involves the attachment of carbohydrates to polypeptide chains, is a natural process. Co-translational or post-translational alterations can be used to achieve this adhesion. The amine group of the asparagine residue causes N-linked glycosylation, which results in the creation of an amide bond. The oxygen atom in the side chain of Ser or Thr residues forms an ether connection with the carbohydrate moiety in an O-linked glycopeptide . Glycopeptides and glycoproteins can be synthesised via chemical and chemo-enzymatic techniques [2].

To circumvent this challenge, convergent (fragment-condensation) approaches such as on-resin linked glycopeptide and Lansbury aspartylation are used as alternatives. Because O-glycosylation is not possible with this method, the convergent approach is mostly employed for N-linked glycopeptide synthesis. The glycosylamine unit is attached to a free Asp residue on a peptide in these convergent approaches by condensation of the amino acid. The main disadvantages of convergent techniques include peptide racemisation at the C-terminus and the production of aspartimides. To alleviate these disadvantages, a number of solutions have been devised. The 2-phenylisopropyl protecting group is employed as an orthogonal handle to produce glycosylation sites on-resin for the coupling of a large high mannose oligosaccharide to peptides to prevent aspartamide production in an on-resin convergent synthesis [3]. Using allyl esters and 4-[N-[1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl]-amino]benzyl (Dmab) as protecting groups on aspartic acid residues improves the yield of N-linked glycopeptides. Glycosylation by chemicals Aside from O- and N-linked glycosylation, several chemical methods for attaching carbohydrate units to different amino acid residues at the N-terminus of the peptide sequence have been developed. One of the examples where the anomeric carbon of the carbohydrate was changed by ethanoic acid and linked to the N-terminus of NAPamide via SPPS is the conjugation of galactose to the N-terminus of -melanocyte-stimulating hormone octapeptide analogue (NAPamide).

Glycosylation by chemoenzyme Chemo-enzymatic methods are effective tools for achieving highly efficient synthesis of complex carbohydrates by combining the flexibility of chemical synthesis with the great regio- and stereo-selectivity of enzyme-catalyzed processes. These methods are particularly well suited to complex chemical synthesis, such as the production of sialic acid-containing compounds or the attachment of oligosaccharides to polypeptides. The most widely utilised enzymes in the chemoenzymatic method are Endo-N-Acetylglucosaminidases (ENGases), glycosyltransferases, and Oligosaccharyltransferases (OST). In a single step, ENGases are able to couple an intact oligosaccharide to a GlcNAc-containing peptide or protein as an efficient acceptor. ENGases have transglycosylation activity, which can attach the released oligosaccharyl moiety to an appropriate acceptor and produce a new glycopeptide, in addition to hydrolysis of the glycosidic bond (cleaving the chitobiose core of N-linked glycans between two GlcNAc residues). Endo-A (from Arthrobacter) and Endo-M (from Mucor hiemalis) are two prevalent ENGases that process oxalines as donors and attach them to GlcNAc derivatives as acceptors, respectively. Endo-A attaches high-mannose N-glycans to a variety of acceptors with GlcNAc residues, whereas Endo-M attaches three different types of N-glycans (high-mannose type, hybrid type, and complex type). Although each enzyme's transglycosylation activity is distinct, their hydrolytic activity often results in product hydrolysis, which limits their use in chemoenzymatic methods [4].

By attaching one monosaccharyl residue at a time, glycosyltransferases can lengthen the sugar chain. -(1,3)-N-Acetylglucosaminyltransferase is a Neisseria meningitides enzyme that was employed to conjugate GlcNAc residues to the lactose moiety of endomorphin-1 and enkephalin derivatives. Another glycosyltransferase developed from Neisseria meningitides, Lipopolysaccharyl-1,4-galactosyltransferase, has been used to bind the galactose unit (Gal) to the terminal lactose residue of lipooligosaccharide. To increase the metabolic stability of the peptide and target the asialoglycoprotein receptor, LgtC was utilised to link the Gal residue to a glycosylated enkephalin (ASGPR). High regio- and stereo-specificity without the requirement for protective groups are among the benefits of utilising glycosyltransferases for glycosyl unit attachment.

It is difficult to separate the glycopeptide substrates from the glycosyltransferase in the reaction mixture in a straightforward manner. The attachment of the polyethylene glycol (PEG) moiety to the N-terminal of Mucin1 (MUC1) via SPPS has been found to be an effective approach for facilitating site-specific enzymatic glycosylation of peptides and recovering the final product. Peptide medicines' physicochemical qualities have a big impact on their pharmacokinetic profile and metabolic destiny in the body. The peptide backbone can be glycosylated to improve its molecular stability and change its shape. It was discovered that modifying hamster prion peptide with other sugar molecules, such as mannose, galactose, and N-acetylgalactosamine (GalNAc), had a variety of effects on the polypeptide chain's structural characteristics. Mannosylation of the prion inhibited the production of amyloid fibrils (a type of aggregation), showing that this sugar item on the prion peptide has an anti-aggregation activity [5]. The position of the glycosyl unit in the peptide structure has been demonstrated to play an essential role in modifying the conformation of the peptide backbone, which may affect the biological properties of the modified peptide. GalNac binding to Thr6 and Thr21 in a calcitonin peptide, for example, disrupted the helical shape of the whole peptide, resulting in decreased receptor binding affinity and bioactivity. Due to enzymatic breakdown, endogenous peptides have short half-lives in the biological milieu. Glycosylation can help peptides with their poor pharmacological characteristics as well as their medicinal efficacy. Position, kind, and amount of carbohydrates are all important elements in enhancing the pharmacological properties of modified peptides and influencing their biological roles. 61 The peptide–receptor interactions, biodistribution, and pharmacological activity of glycosylated peptides can all be influenced by the position of the glycosyl unit linked to the peptide. Due to enzymatic breakdown, endogenous peptides have short half-lives in the biological milieu. Glycosylation can help peptides with their poor pharmacological characteristics as well as their medicinal efficacy. Position, kind, and amount of carbohydrates are all important elements in enhancing the pharmacological properties of modified peptides and influencing their biological roles [6]. The peptide–receptor interactions, biodistribution, and pharmacological activity of glycosylated peptides can all be influenced by the position of the glycosyl unit linked to the peptide. When carbohydrate units are linked to peptides in the correct position, the native peptide's affinity for the target receptor is preserved, allowing the peptide to be orally active. For O-glycosylated calcitonin analogues, the site-dependent effect of glycosylation was examined, and it was discovered that glycosylation changes both the conformation and biological activity of calcitonin in a site-dependent manner. In rats, the effect of different carbohydrates on renal vasopressin delivery was investigated. The glucosylated and mannosylated vasopressin had higher renal absorption than the galactose-modified equivalent, which resulted in lower peptide clearance. In vitro, the glucosyl and mannosyl conjugates were found to be selectively attached to the kidney microsomal membrane, enhancing the peptide's renal absorption [7].

Glycotargeting, also known as carbohydrate-mediated delivery, is a method that uses cell surface recognition to target certain organs. Carbohydrates are good candidates for receptor-targeted peptide administration because their receptors, called lectin receptors, are found in the membranes of a variety of cells, including liver, tumour, and kidney cells. As a result, medicinal compounds that have been conjugated with carbohydrate units can be recognised by those receptors and internalised into cells. ASGPR is a lectin receptor that recognises galactose and galactosyl residues in glycoproteins and is expressed on the surface of liver hepatocytes. Peptides can be delivered to hepatocytes by targeting ASGPR. According to reports, glycotargeting can potentially be used to target the kidneys and the brain [8].

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