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REVIEW ARTICLE

Development of Peptide-based Nanotubes with Increased Resistance to Enzyme Degradation

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ABSTRACT: This systematic literature review evaluates strategies for enhancing proteolytic resistance in peptide-based nanotubes (PBNTs), self-assembling cylindrical nanostructures with therapeutic potential in drug delivery applications in medicinal treatments such as drug delivery. The primary focus is on chemical and structural modifications of drug molecules that improve PBNT stability in vivo, along with discussion on the mechanisms, limitations, strengths, and implications of each strategy, as well as future therapeutic applications. The review also highlights the need to integrate multiple strategies to achieve different functionalities needed for a specific drug application. Further research should include in vivo studies and computational modeling via machine learning to validate these strategies and refine PBNT performance. This review additionally emphasizes the critical need for developing PBNT carriers that are both durable and functionally versatile for the field of medical therapeutics. This article is based on qualitative research utilizing peer-reviewed articles, journals, and various studies from the 2000s.
KEYWORDS: Biochemistry, Medical Biochemistry, Peptides, Degradation Enzymes Resistance, Nanotubes.

Introduction

The field of drug delivery focuses on how therapeutic compounds can make their way throughout the body. Despite significant advances in pharmaceutical sciences, several limitations persist in contemporary drug delivery systems. These include the lack of precise targeting, poor bioavailability, cytotoxicity, and complicated administration, which can limit the efficacy of the drug.1 Recently, nanotechnology has shown promise as a tool to develop more precise and efficient drugs. In particular, peptide-based nanotechnology has become an emerging topic in the field of drug delivery. Due to their unique properties, including enhanced bio-barrier permeability, self-assembly, and precision-guided delivery, it holds strong promise for future medical applications.[1-3]

In recent years, researchers have focused on designing nanostructures that resemble biological molecules and can serve similar functions. Peptides are widely viewed as a viable solution for this. Their versatility and amino acid building blocks allow for tunable chemistry. This modular chemistry allows researchers to choose how they interact with various cells in the body.[4]

Peptides are polypeptide chains of 50 or fewer amino acids. They have shown tremendous potential to treat diseases such as cancer, cardiovascular disease, and diabetes, but many challenges still exist: low oral bioavailability, short half-lives, and enzymatic susceptibility.[12] Structurally, peptides are chains of amino acids with an amino group called the N-terminal at one end, and a carboxyl group called the C-terminal at the other. Amino acids grow by forming a peptide bond between the C-terminal and the amino group of a free amino acid.[13] Peptides can then be gathered into different types of nanostructures, such as hydrogels, nanotapes, nanonecklaces, nanofibers, as shown in Figure 1.[14] Peptide-based nanotubes are composed of cyclic, disk-shaped peptides and have shown the ability to self-assemble under certain conditions.[6,19]

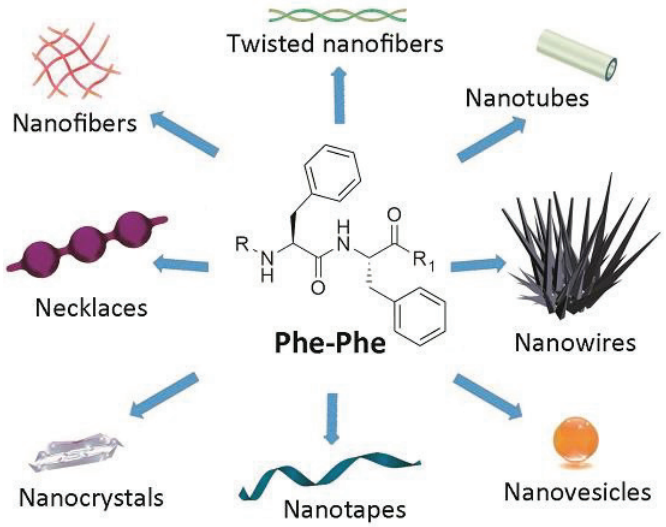

Figure 1: Graphical representation of the different types of nanostructures.[41]

The formation of peptide nanotubes can come from molecular self-assembly that allows the peptide to align in specific organizations, reducing system free energy and increasing molecular stability. Hydrogen bonding is one of the key forces to drive self-assembly. For PBNTs specifically, they create a path for tubular assembly. A cluster of peptide molecules is chosen as a "seed," and others branch off from the main sequence, making the process highly sequence dependent. Changes in pH, temperature, and solvent polarity can all influence the kinetics of peptide self-assembly. It has the potential to provide a modular framework for designing adaptive biomaterials in medicine.[16]

Despite all the advantages of peptide nanotechnology, one of their most widely recognized challenges is their susceptibility

DOI: 10.36838/IJHSR816.73

to enzymatic degradation by proteases.[5] However, a specific type of peptide nanoparticle, called a peptide-based nanotube (PBNT), could be used with different strategies to increase proteolytic resistance.[5,6] PBNTs are well-defined hollow cylinders with a diameter range of 0.5–500 nm and an aspect ratio greater than 5.[6] This type of structure makes them easily modifiable, which can be used to increase proteolytic resistance.[6] While various strategies like cyclization, side-chain modification, and conjugation have been explored in peptides, not many studies have focused narrowly on PBNTs.[5] This highlights a critical gap for research in PBNTs that can safely and effectively circulate throughout the body.[6]

From a chemical perspective, peptides should take several hundred years to fully hydrolyze on their own. However, the degradation of peptides *in vivo* occurs when Proteolytic enzymes recognize specific amino acid sequences and catalyze the hydrolysis of peptide bonds, resulting in peptide fragmentation and loss of biological activity. The rate at which this degradation occurs is affected by factors such as the conformation of the peptide, the amino acid sequence, and the accessibility of the bonds to the protease. In summary, the degradation of peptides and PBNTs is facilitated by proteases acting as a catalyst in the hydrolysis of peptide bonds.[7]

Addressing this weakness in PBNTs can lead to a variety of benefits, such as antiviral effects, gene delivery, and improved drug delivery.[8] Specific PBNTs are able to inhibit viral replication. This mechanism may enable the inhibition of influenza A virus replication and other viral diseases.[9] Moreover, their unique tubular structure allows the inner section to hold drugs while the outside can be modified or functionalized for targeting specific receptors or shielding from enzymes.4 Other types of PBNTs have been proven to reduce harmful activity in a corneal injury model via gene therapy and even have the potential to be ingested orally and carry DNA to other tissues in the body.[10] Research also demonstrates that PBNTs effectively deliver anticancer drugs with controlled release due to their hollow nature.[11] Developing strategies to protect nanotubes from proteolytic breakdown would expand their use across many diverse fields of medicine, including but not limited to: immunotherapy, regenerative therapy, and controlled release systems.

Beyond direct medical applications, PBNTs also offer a new way of thinking about modern medicine. They offer a more modular approach, allowing researchers to fine-tune drugs from the top down. This approach could offer doctors and scientists more control over how their medicine would act *in vivo*. Therefore, further research work is warranted to expand the creation of optimized PBNTs for various physiological conditions. This research study will recommend methods to fully utilize the potential of PBNTs by increasing their proteolytic resistance within the body. By examining strategies used to modify other types of peptides, this paper will compare and apply their methods to nanotubes instead, evaluating which modifications will be the best suited for maintaining structural integrity *in vivo*. No lab work or clinical trials will be done. Instead, this paper will use hypothetical and logical explanations based on existing knowledge of peptide chemistry and nanostructure design. This review narrows down the topic of peptides to only PBNTs due to their superior proteolytic resistance, aiming to provide a framework for future experimental investigations that could translate these strategies into practical applications.

Methodology

This work is a literature review, not an experimental investigation. All data were derived from secondary, peer-reviewed sources, rather than laboratory experimentation. The purpose of this approach was to evaluate existing findings rather than to find new data. A comprehensive review method was used to effectively provide a complete understanding of current advancements, limitations, and potential directions for PBNT use in the future, as it relates to biomedical contexts.

To conduct this review, a literature search was carried out using databases like PubMed and Google Scholar. Additional databases such as ScienceDirect and Scopus were also included to ensure coverage of nanotechnology and biomedical publications. The temporal scope was restricted to publications from 2015 to 2025 (except cited refs. 6 and 13) to ensure current relevance. Search terms including 'peptide nanotubes,' 'drug delivery,'... were combined using Boolean operators to gather information on the nanotubes, peptides, applications, and ways to increase proteolytic resistance. This data on peptides was applied to PBNTs to see how similar methods could be used to increase their proteolytic resistance.

The initial searches came up to around 5000 papers in total. However, after removing duplicates and scanning through titles and abstracts for relevance, a final set of 20 studies was selected for an in-depth review. Papers that didn't mention or reference PBNTs weren't included. Further papers were manually included to provide context or collected from papers already found.

Inclusion criteria included addressing PBNT or related peptide nanostructures, addressing biomedical or therapeutic applications, and being peer-reviewed in English. Papers that were excluded were lacking primary data, specificity to PBNTs, or clarity. Only original research articles, literary reviews, and studies with clear and methodical reporting were included. Studies without a clear context were removed to maintain academic rigor.

No physical instruments, materials, or laboratory techniques were used. As this study relied on publicly available academic publications, no ethical approval or considerations were necessary.

Because this study did not involve human or animal subjects, ethical review was not necessary. However, academic integrity protocols were strictly followed, including accurate citations, avoidance of plagiarism, and evaluation of each source's credibility and quality.

Analysis highlighted several techniques to increase enzymatic resistance within PBNTs, such as cyclization, D-amino substitution, and chemical capping. Furthermore, the research revealed that PBNTs showed great promise in therapeutic applications. Beyond highlighting existing research and identifying trends, this review aimed to synthesize the findings into

a conceptual and easy-to-understand guide for future peptide design and study.

A limitation of this research is that it is mostly hypothetical. There is a lack of existing laboratory research focusing on increasing proteolytic resistance in PBNTs or even peptides in general. Most current studies focus on structural formations or early-stage degradation. Few explore long-term behavior or effects *in vivo*.

However, by identifying clear mechanisms to increase proteolytic resistance in PBNTs, this paper could provide a foundation for future work for improved PBNTs.

■ Structural Designs and Proteolytic Resistance Strategies

The characteristics of PBNTs come from the sequence, chemical composition, and modifications of their peptide building blocks. They dictate their self-assembly, morphology, and functional potential. Self-assembling peptides derive from single amino acids, dipeptides, cyclic peptides, D/L peptides, and functional or lipidated variants. They provide tunable structural characteristics.[8,17,18] Cyclic peptides form PBNTs by stacking on top of each other, with amino and carbonyl groups faced perpendicular to the ring, stabilizing the structure through hydrogen bonding between the oxygen in the carbonyl group and the nitrogen in the amino group. When alternating D- and L-type amino acids, the symmetry allows them to stack neatly and form a PBNT.[19] Dipeptides, a peptide made from 2 amino acids, are the shortest and simplest form of peptides. To self-assemble, they need 2 hydrophobic amino acid residues and hydrogen bonding. Intermolecular forces, such as π-π stacking, Van Der Waals forces, and hydrogen bonding, let dipeptides form a nanotube shape.[4] Lipidated peptides, also known as lipopeptides, are hydrophobic oligopeptides with attached lipid chains that make the whole molecule amphiphilic.[20] A study by Castelletto *et al.* showed how a lipopeptide (C16KTTβAH) could self-assemble in water due to its lipid tail and potentially have selective anti-cancer effects.[21] Single amino acids could be modified and self-assembled for drug delivery or other therapeutic applications such as cell culture, photocatalysis, and antibacterial applications. They can also possess fast self-assembly kinetics and excellent physical and chemical properties; however, the peptide may lose aspects of its biological function, such as the ability to form metal complexes or its antimicrobial properties.[22,23]

Key strategies for controlling PBNT structure include taking advantage of cyclization and heterochirality. Cyclic peptides form β-sheet-like tubular structures, with the peptide backbone inside the tube and side chains exposed on the outside. This lets us control nanotube diameter, surface chemistry, and rigidity, while increasing proteolytic resistance.[17,18,24] Cyclization is one of the most promising strategies. It constrains the peptide backbone, reduces flexibility, and limits enzymatic access points. Empirical evidence demonstrates that conformationally constrained peptides exhibit enhanced receptor binding affinity and enzymatic resistance.[17] Peptide nanotubes are formed from stacking amino acid monomers. Linear monomers could be used, but they have less proteolytic resistance compared to cyclized monomers. Through cyclization and the exploitation of heterochiral amino acid properties of amino acids, alternating types of amino acids could be used to form a PBNT with more rigidity and enzymatic resistance than one composed of linear monomers.[6] Cyclization comes in four forms: head-to-tail, head-to-side chain, side chain-to-side chain, and tail-to-side chain. Head-to-tail cyclization leads to rigid peptide structures and predictable assembly, while also blocking off free N- and C- termini that proteases attach to, increasing proteolytic resistance.[25] Furthermore, a study by Clover *et al.* showed that by substituting D-amino acids for L-amino acids, it could influence the molecular-level packing and the supramolecular morphology, increasing rigidity and the location of termini, potentially increasing proteolytic resistance.[26] However, it could potentially lose its ability to bind to metal receptors or metal binding affinity.[27]

Chemical modifications like capping the N-terminal, halogenation, and side-chain analogs can enhance π-π stacking, making the PBNT more rigid.[3,4,18] While also stabilizing the structure, they can increase functionality by adding more sites for functionalization. Separate studies by Vernon and Wener showed that capping aromatic groups on the N- and C- termini of proteins led to more π-π stacking, which could increase rigidity and make it harder for proteases to attach to and cleave backbone bonds.[28,29] -Halogenation is the process of introducing halogens into a chemical compound. When used in peptides, they have the potential to increase proteolytic resistance; however, they cannot be generalized. It depends on the substitution position and the number of halogens introduced.[30] Furthermore, a study by Glibowicka *et al.* showed that Lys-chain shortening could protect against enzymatic degradation. By making the terminal amine side chain shorter and less flexible, the target site could become hidden and less accessible to the protease, increasing proteolytic resistance.[24]

To further extend stability, other types of backbone modifications could be utilized. N-terminal acetylation, C-terminal amidation, and incorporation of D-amino acids could increase enzymatic resistance.[31] It would be especially useful for PBNTs, where exposed terminal points could let the protease interact with them.

N-terminal acetylation is where an acetyl group (-$COCH_3$) is added to the first amino acid of a peptide or a protein, the α-amino group.[32] If PBNTs are Nt-acylated, they could potentially resist enzymatic cleavage or degradation, because they could block flagging for degradation from E3 Ub ligases.[33] Moreover, a study by Kang *et al.* showed that Nt-acetylation prevented enzymatic degradation.[34] C-terminal amidation is replacing the free carboxyl group (-COOH) at the C-terminal end of the peptide with an amide group (-$CONH_2$). This has been shown to enhance structural stability and antimicrobial activity.[34,35] On the other hand, D-amino acids are enantiomers of more commonly occurring L-amino acids. Given the stereoselectivity of human and microbial proteases for L-amino acids, substituting them with D-amino acids in PBNTs could lead to enhanced peptide stability against protease degradation.[34]

DOI: 10.36838/IJHSR816.73

Additionally, encapsulation could be used to create a protective barrier around bioactive peptides. Literature indicates liposomal encapsulation as an optimal strategy because of its bioavailability, non-toxicity, and amphipathic characteristics.[36] Since liposomes are also lipids, they are biocompatible and thus considered safe by the Food and Drug Administration (FDA).[37,38] Liposomes also promote targeting of diseased cells.[38]

A summary of the stabilization strategies for PBNTs and their relative advantages and limitations is shown in Table 1. Overall, each strategy aims to enhance stability, but comes with its respective advantages and limitations, implying that the purpose of the peptide must be considered when choosing a strategy.

Table 1: Summary of stabilization strategies for peptide-based nanotubes (PBNTs) and their relative advantages and limitations.

Strategy	Mechanism	Advantages	Limitations
Cyclization	Constrains the peptide backbone	Enhances rigidity and proteolytic resistance	Could hinder self-assembly or biological activity in PBNTs
D-amino incorporation	Alternating D- and L-amino acids improves symmetry and stacking	Increases packing and provides proteolytic resistance	Could hinder functional activity such as metal binding
N-terminal acetylation	Adds acetyl group on α-amino group	Enhances proteolytic resistance	Could affect functional impact
C-terminal amidation	Replaces -COOH group with -CONH2	Enhances proteolytic resistance	Could affect functional impact
Halogenation	Adds halogen atoms onto the peptide chain	Could increase rigidity and proteolytic resistance	Effects not easily predictable; not enough research
Aromatic capping	Caps aromatic groups onto N- and C- termini of proteins	Enhances π-π stacking, improves rigidity	Can alter self assembly into nanotubes
Lipidation	Attach lipid chains onto peptide	Increase self-assembly properties and possibly give anti-cancer effects	Could reduce solubility and cause aggregation
Single amino acid modifications	Modify individual residues	Allows for fine control	Impacts may be hard to predict
Encapsulation	Surrounds peptides with carriers like liposomes	Improves stability, bioavailability, and targeted delivery	May impact release rate

■ Therapeutic Applications of PBNTs

Drug delivery is one of the most promising applications of PBNTs. Their hollow cylindrical structure lets small molecule drugs be efficiently encapsulated, and the modifiable peptide backbone allows for chemical functionalization, which can add many helpful properties, such as controlled release, targeting specificity, and biocompatibility. Studies suggest therapeutic precision while minimizing potential harmful side effects.[3,4]

Studies show that PBNTs can deliver anticancer drugs with enhanced selectivity and reduced off-target toxicity. Since the proteins on tumor cells often differ from those of normal cells, using strategies like phage display could be used to find those specific proteins and molecular markers. Once they are found, specific PBNTs carrying cytotoxins could bind to the surface of the affected cell. This suggests an increase in the efficacy of the drug and a reduction of unwanted effects on normal cells.[39]

Functionalized nanotubes could be used to cross biological barriers and carry DNA or RNA cargos. This demonstrates potential in localized and systemic administration. Because of their interchangeable surface chemistry, PBNTs could be used to selectively target nucleic acids, which may protect them from degradation and enable targeted release within cells. These studies suggest PBNTs can protect the DNA from acid, bile, and enzymes, and improve permeability and stability, letting it reach many different tissues.[8]

Studies show that some PBNTs can interfere with the pathway to viral reproduction. They can block viral entry or replication machinery.[31] This suggests that PBNTs could be used for broad antiviral therapy. A study by Montero *et al.*[40] discovered cyclic peptides with anti-hepatitis C virus (HCV) activity. The specific characteristics needed for anti-HCV activity include chemical and structural modifications, a cyclic backbone configuration, and a pattern of basic and acidic amino acids in the peptide sequence.[40]

Self-assembling peptides in corneal injury models have been shown to reduce harmful activity through controlled gene expression and bioactive delivery. This is especially significant since the epithelial layer, which restricts molecular entry in normal drugs, has been bypassed. This implies that some PBNTs with similar structures could distribute to the duodenum, liver, stomach, and kidneys.[10]

Finally, to address the growing problem of antibiotic resistance in bacteria, cyclic peptides could offer a promising alternative. Peptides with amphiphilic properties, meaning they have both hydrophilic and hydrophobic regions, are particularly effective. In fact, studies have shown that even a single substitution of an amino acid with one containing hydrophilic elements can significantly enhance antibacterial activity. This modification has been effective against several bacterial strains, including MRSA, *E. coli, U. linza*, and *N. perminuta*, demonstrating that small changes in peptide composition can have a substantial impact on antimicrobial properties and suggesting that cyclic peptides could be further optimized as novel antibacterial agents.[8] This suggests PBNTs, which are very similar to cyclic peptides structurally, could have the same effects.

■ Discussion

This review explored ways to enhance enzyme resistance in PBNTs and lists various viable methods. Cyclization, β-sheet cyclization, and terminal protection are recognized as means to achieve increased PBNT stability. Chemical modifications such as side-chain modifications and the addition of noncanonical amino acids further reduce enzymatic degradation and improve the half-life of these nanotubes in biological environments. For treatment, PBNTs work well for drug and gene delivery, antiviral and regenerative applications, and self-assembly. Beyond the main results, a key takeaway is how closely tied these factors are. Minor molecular modifications, such as D-amino incorporation or N-terminal acetylation, can drastically affect the chemical properties of the PBNT. Thus, each sequence of the PBNT must be precisely aligned with the desired functional outcome of the drug.

Furthermore, the findings of this study suggest that proteolytic resistance strategies could be highly dependent on the environment in which the drug is used. Different types of treatments would each require specific modifications of the PBNT. In some ways, this could be considered a strength of PBNTs, seeing how they can be readily adaptable to many different scenarios.

Through review of the limitations and strengths of the methods for increasing proteolytic resistance, Cyclization represents the optimal strategy for PBNT stabilization, as it simultaneously enhances proteolytic resistance through backbone constraint while maintaining favorable self-assembly characteristics. D-amino substitution, N-terminal acetylation, and C-terminal amidation also stand out as notable methods to increase enzymatic resistance. D-amino substitution and cyclization could be combined to develop PBNTs with increased resistance and self-assembly properties, although more research is needed to ensure no adverse effect on functional ability. Finally, N- and C- terminal modifications could lead to an increase in enzyme resistance as well as functional activity.

The implications are that PBNTs could become a useful, customizable, and versatile tool in therapeutics, especially if research focuses on the *in vivo* stability of PBNTs. However, more experimental work that focuses on computational modeling and laboratory experiments would be needed for PBNTs to be used in medicine.

■ Conclusion

This review article discusses the potential benefits and drawbacks of different drug molecule modification strategies and highlights the need for adopting the integration of multiple strategies to meet specific drug therapeutic applications. Considering all the various factors, the author concludes that cyclization may serve as a foundational design strategy for peptide-based nanotubes (PBNTs), yielding highly predictable structural dynamics conducive to machine learning integration for forecasting stability and efficiency. Furthermore, the modular architecture of cyclized PBNTs facilitates the conjugation of functional moieties, enabling the development of sophisticated, stimuli-responsive systems with expanded therapeutic potential.

In summary, advancing PBNT design through chemical and structural means could overcome one of the main barriers in peptide-based drug delivery and bring emerging nanotechnology into therapeutics.

■ Acknowledgments

I would like to thank Professor Kristina Lilova of Arizona State University and Professor Virgel Torremocha of the University of Southeastern Philippines for their mentorship during this writing process.

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