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Amyloid-β Inhibiting Peptides: An Innovative Strategy for Alzheimer's Disease Treatment

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ABSTRACT

Alzheimer's disease (AD), the most common neurodegenerative disorder, is characterized by the accumulation of amyloid-β (Aβ) plaques, leading to progressive cognitive decline. Targeting Aβ aggregation has become a major therapeutic focus, and peptide-based inhibitors have emerged as a promising approach due to their ability to specifically bind to Aβ and prevent its toxic oligomerization and fibril formation. This review discusses the advancements in Aβ-inhibiting peptides, including those derived from the Aβ sequence, as well as novel peptides discovered through phage display and mirror-image phage display technologies. These peptides offer significant advantages such as high selectivity and lower neurotoxicity, making them attractive candidates for therapeutic development. However, critical challenges—such as enzymatic degradation, poor blood-brain barrier (BBB) penetration, and the tendency for self-aggregation—have limited their clinical application. To overcome these barriers, recent innovations such as the incorporation of D-amino acids, cyclization, and retro-inverso modifications have improved peptide stability and bioavailability. Despite these improvements, further research is essential to optimize peptide design, enhance BBB permeability, and ensure long-term efficacy. This review emphasizes the importance of rational peptide design and the development of advanced delivery systems to address these limitations. By refining the molecular interactions and pharmacokinetic properties of Aβ-inhibiting peptides, future studies could significantly enhance their therapeutic potential. Ultimately, these efforts aim to advance peptide-based treatments through clinical trials and bring about meaningful progress in AD therapy.

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Introduction

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder, primarily marked by the gradual deterioration of cognitive functions such as memory and executive skills. Despite substantial advancements in research, a definitive cure for the AD has yet to be identified [1, 2]. It is currently estimated that more than 50 million people worldwide are living with AD and this number is expected to increase to 152 million by 2050, with a global economic burden of $1.1 trillion [3, 4]. A key hypothesis that is widely accepted in understanding the pathogenesis of AD is the amyloid cascade hypothesis. This hypothesis proposes that the accumulation of amyloid-β (Aβ) fibrils and their deposition in amyloid plaques are key events in the initiation of AD. These events cause subsequent pathological processes such as tau protein hyperphosphorylation, oxidative stress and chronic inflammation [5-7]. Aβ plaques are mainly composed of Aβ peptides, which have a molecular weight of approximately 4 kDa and are generated by proteolytic cleavage of the amyloid precursor protein (APP) [8]. The two most common isoforms of Aβ are Aβ40 and Aβ42, with Aβ42 being more neurogenic despite the abundance of Aβ40 [9-11]. Over time, these peptides aggregate to form oligomers, protofibrils, and mature fibrils, eventually leading to the formation of Aβ plaques that accumulate in brain tissues and cerebral blood vessels. These deposits are closely related to neuroinflammation and nerve death [10-12].

Research indicates that Aβ accumulation in the brain likely represents the earliest pathological event, occurring years before the clinical symptoms of AD become evident [13, 14]. As a result, various diagnostic agents have been developed to detect Aβ deposition in the brain long before the onset of symptoms [15, 16]. Given this, inhibiting the aggregation of Aβ peptides and promoting their clearance have emerged as critical strategies for AD treatment. Among the approaches explored are the use of organic small molecules [17] and peptide-based inhibitors [18, 19]. Peptides, due to their high binding affinity for Aβ and lower toxicity, are regarded as more promising therapeutic candidates compared to small molecules [20].

Based on this knowledge, peptides offer significant potential as therapeutic agents to inhibit Aβ accumulation, reduce Aβ-induced neurotoxicity, and facilitating the early diagnosis of AD [20]. In this review, we investigate the therapeutic potential of peptide-based inhibitors against Aβ aggregation and discuss strategies to overcome the challenges in this field of research.

Peptide-based Therapeutics

Therapeutic peptides have gained prominence as a versatile and impactful class of bioactive compounds, playing key roles in various physiological functions such as hormones, growth factors, neurotransmitters, ion channel ligands, and anti-infective agents [21]. These peptides demonstrate a remarkable ability to bind with cell surface receptors, initiating precise intracellular signaling pathways due to their high specificity and affinity [22, 23]. Compared to biologics like proteins and antibodies, therapeutic peptides offer distinct advantages, particularly their lower immunogenicity and cost-effectiveness in production [24, 25]. In contrast, small molecule drugs have traditionally dominated therapeutic treatments because of their advantages, including lower production costs, ease of oral administration and effective membrane penetration. However, small molecules suffer from a significant drawback—limited specificity. Their small size often leads to off-target effects, as seen with tyrosine kinase inhibitors like sorafenib and sunitinib, which not only inhibit VEGF receptors to exert anti-angiogenic effects but also affect other kinase receptors, leading to cytotoxicity [26, 27]. Therapeutic peptides, with their larger size and flexible structures, generally provide greater selectivity, making them more effective at inhibiting large protein-protein interactions, a critical aspect of treating complex diseases [28]. Despite these advantages, therapeutic peptides are not without their challenges. Their limited membrane permeability and instability in vivo hinder their ability to target intracellular molecules effectively. More than 90% of peptide drugs currently in development are aimed at extracellular targets because of difficulties in crossing the cell membrane [21]. Furthermore, the natural composition of peptides makes them vulnerable to rapid enzymatic degradation, leading to a short half-life and limiting their therapeutic potential [29]. To overcome these limitations, ongoing research focuses on innovative solutions, including chemical modifications and advanced delivery systems, aimed at improving peptide bioavailability, stability, and intracellular targeting.

The growing interest in peptide-based drugs has extended to several critical disease areas, with AD being a prominent example [15, 16]. Peptides, which are chains of two to one hundred amino acids, are gaining attention in AD treatment because of their ability to selectively target Aβ peptides [30-32]. Aβ peptides play a central role in forming amyloid plaques, which contribute to neurotoxicity and neuron degeneration in AD. Modifications such as incorporating D-enantiomer amino acids, cyclic structures, and other chemical alterations have

been shown to enhance peptide stability, improve BBB permeability, and reduce enzymatic breakdown, making these peptides promising candidates for AD therapy [20, 33]. To date, more than 400 peptide-based drugs are undergoing clinical trials, with 60 already receiving regulatory approval [31, 34, 35]. However, challenges remain, particularly in improving their stability under physiological conditions and increasing their specificity for disease-related targets. Nevertheless, the continued development of structurally modified peptides presents immense promise, especially in addressing complex conditions like neurodegenerative disorders [20, 36]. In conclusion, while therapeutic peptides must overcome challenges related to stability and permeability, their unique ability to combine selectivity with adaptability makes them powerful tools in modern drug development. Their expanding role, particularly in the treatment of diseases like AD, underscores their potential to revolutionize precision medicine, offering innovative solutions for previously untreatable therapeutic targets [37].

Amyloid-β (Aβ)-inhibiting Peptides

Aβ-inhibiting peptides are generally classified into two main categories: The first category includes peptides that are designed based on the sequence of Aβ itself and are specifically used to inhibit the aggregation of Aβ peptides. These peptides are usually inspired by key sequences in Aβ peptides and have been improved through molecular engineering to efficiently interact with the aggregation-prone regions of Aβ [38-40]. The second category comprises peptides identified and designed using the phage display technique. In this method, millions of different peptides are displayed by phages, and those with the highest affinity for binding to Aβ are selected and subsequently optimized to maximize their inhibitory properties. These peptides have been proposed as valuable tools in AD research and treatment due to their high accuracy and selective ability to target Aβ [41-43]. Table 1 presents a list of selected Aβ-inhibiting peptides that have been designed using both methods.

Aβ-inhibiting Peptides Derived From the Aβ sequence

In a study by Lührs et al. the fibril structure of Aβ42 was experimentally described for the first time [72] and several key regions in this structure were identified for effective interactions that could be used to design Aβ-inhibiting peptides [60]. These regions include two hydrophobic segments (residues Ala30 to Val36 in the C-terminal and Lys16 to Ala21 in the N-terminal) and a hydrophilic region with electrostatic interactions (between Asp23 and Lys28) [73, 74]. These regions play a vital role in Aβ nucleation and fibril formation, making them ideal targets for designing Aβ peptide inhibitors [10, 75]. Peptides designed based on these regions bind to specific sites on Aβ and prevent its aggregation into amyloid fibrils.

However, peptides containing natural amino acids face challenges due to rapid enzymatic degradation and a tendency for self-aggregation [76]. To address these issues, strategies such as incorporating D-amino acids, cyclization, retro-inverso analogs, fluorination, and N-methylation have been employed [77, 78]. D-peptides, which show greater protease resistance and higher affinity for Aβ, have demonstrated better inhibition of Aβ aggregation in animal models compared to L-peptides [55]. Retro-inverso peptides, which are composed of D-amino acids in a reversed sequence, have shown enhanced protease resistance, improved BBB permeability, reduced self-aggregation, and more effective inhibition of Aβ aggregation [79]. Other successful strategies include methylation of amide groups, cyclization, and the use of fluorinated amino acids, which have shown stronger inhibition of Aβ aggregation and higher resistance to enzymatic degradation [80, 81].

It has been reported that peptide-based inhibitors derived from the Aβ sequence 17-21 (LVFFA) play an important role in inhibiting Aβ aggregation by binding to Aβ and preventing fibril formation [82, 83]. For example, peptide LK7 (Ac-LVFFARK-NH_2) has demonstrated dose-dependent inhibition of Aβ42 fibrillation, though its tendency for self-aggregation has led to cytotoxicity [49]. To improve solubility and reduce self-aggregation, researchers have linked this peptide to beta-cyclodextrin and used poly (lactic-co-glycolic acid) nanoparticles (NPs), which increased its Aβ-binding affinity and aggregation inhibition [49, 84]. Additionally, head-to-tail cyclization of the LK7 peptide has been shown to reduce self-aggregation, enhance Aβ binding, and improve proteolytic stability in serum [85]. A modified version of LK7, called LK7-HH, which includes two histidine residues, has been found to reduce reactive oxygen species (ROS) production and aid in copper ion binding [86]. Another peptide inhibitor, iAβ5, designed based on the Aβ sequence 17-21 (LPFFD), inhibits Aβ aggregation by preventing intramolecular hydrogen bonds in fibrils, as the lack of a proton on the proline nitrogen disrupts peptide bond formation [69, 87]. However, due to its rapid enzymatic degradation and limited BBB penetration, iAβ5 has been modified by methylation of the nitrogen between residues of proline and phenylalanine, increas-

Table 1. Classification of Aβ-inhibiting peptides based on design strategy

Phage Display-based Peptides	Type	Ref.	Aβ Sequence-based Peptides	Type	Ref.
Ac-FYLKVQSLHHHH-NH_2, designed based on common phage display	L	[44]	LPFFN	L	[45]
RGPRGRV, designed based on Common phage display	L	[46]	KLVFWAK	L	[47]
PYRWQLWWHNWS, designed based on Common phage display	L	[48]	LK7/LVFFARK	L	[49]
RFRK, based on common phage display	L	[50]	RR/RYYAAFFARR	L	[51]
XD4/PIKTLPM, designed based on Common phage display	L	[42]	KLVFF	L	[52, 53]
KH/KSILRTSIRHTH, based on common phage display	L	[54]	PGKLVYAKKLVFFARRRRA	L	[55]
AOEP2/FDYKAEFMPWDT, designed based on Common phage display	D	[56]	LPYFD	L	[57]
ZAβ3 affibody, designed based on common phage display	L	[58]	Diazirine-equipped cyclo-KLVF (b-Ph) F		[59]
GABA-FPLIAIMA, designed based on LIAIMA peptide and molecular docking studies	D	[60]	H102/HKQLPFFEED	L	-
S1/PQVGHL	L	[61]	Fc-KLVFF	L	[62]
pep1/LIAIMA, based on common phage display pep2/IFALMG	L	[63]	Gly (Allyl-RCM)-Xaa-Tyr (Allyl-RCM)	-	[64]
D-pep or D1/QSHYRHISPAQV, designed based on mirror image phage display	D	[65]	D (KLVFW)-aminobutyric acid (Aib)	D	[66]
D3 / RPRTRLHTHRNR, designed based on mirror image phage display	D	[67]	iAβ5/LPFFD	L	[68–70]
-	-	-	OR1/RGKLVFFGR OR2/RGKLVFFGR-NH2	L and D	[71]

ing its stability [88]. Both in vitro and in vivo studies have shown that this modified peptide retains its inhibitory activity against Aβ fibril formation, with increased protease resistance and stronger Aβ-binding stability, as supported by molecular dynamics simulations [88]. Peptide KLVFWAK, derived from the Aβ sequence 16-22 (KLVFFAE), replaces residues of phenylalanine and glutamic acid with residues of tryptophan and lysine to enhance solubility and inhibit self-aggregation through electrostatic repulsion [47]. This peptide selectively targets the C-terminal of Aβ oligomers and exhibits less self-aggregation compared to its counterpart, KLVFF, while showing stronger affinity for Aβ aggregates and fibrils [47].

Retro-inverso peptides OR1 (RGKLVFFGR) and OR2 (RGKLVFFGR-NH_2), designed by adding residues of arginine and glycine to the KLVFF sequence, improve solubility and enzymatic stability. However, only OR2 has demonstrated inhibition of Aβ oligomer formation [71]. OR2 was further modified by acetylating its C-terminus (RI-OR2), which preserved its inhibitory activity and enhanced proteolytic resistance in vivo [89]. In another study, RI-OR2 was conjugated with the cell-penetrating peptide (CPP) TAT, which improved its cellular uptake and BBB permeability [90]. CPPs are short cationic peptides known for their ability to cross cell membranes, making them effective tools for delivering drugs across the BBB [91]. Although CPPs are not specifically bound to certain receptors, they are widely used for the targeted delivery of various cargoes across cellular membranes [92]. One of the first reported CPPs, TAT, is widely recognized for its strong cell-penetrating ability [93]. RI-OR2-TAT has been shown to reduce Aβ aggregation, amyloid plaque levels, and oxidative damage while promoting the formation of new neurons in the brain [90].

Peptides IIGLMVGGVVIA and VVIA, derived from the C-terminal of Aβ42, interact with Aβ42 monomers and small oligomers, particularly at the N-terminal [94]. Studies have shown that VVIA-NH_2 can inhibit Aβ aggregation at micromolar concentrations and protect synaptic activity; however, acetylated Ac-VVIA did not exhibit these effects [95]. The non-acetylated VVIA-NH_2 specifically interacts with the C-terminal, while

Ac-VVIA shows a more dispersed binding distribution. Ac-IGLMVG-NH_2 has shown moderate efficacy in preventing Aβ aggregation [96].

Aβ-inhibiting Peptides Derived From Phage Display

Phage display technology is a widely used and powerful method for screening diverse peptide libraries to identify specific, targeted peptide sequences [97, 98]. This technique has revolutionized the discovery of therapeutic peptides, enabling researchers to identify promising peptide candidates by exploiting the binding affinity between the created peptides and a target molecule, paving the way for further investigation into their therapeutic potential [99, 100]. In the field of AD, phage display has played a crucial role in identifying inhibitory peptides against key targets such as Aβ, offering new and promising therapeutic strategies [101, 102]. In this method, extensive peptide libraries are displayed on the surface of phages (viruses that infect bacteria) [100] and these libraries are then exposed to the target molecule. Peptides with the highest binding affinity to the target are selected [103, 104]. This precise selection allows researchers to identify potential therapeutic peptides that can serve as targeted and effective drugs for AD treatment [105]. Peptides derived from phage display are promising for clinical applications due to their high specificity and strong selectivity [100-102]. However, challenges such as susceptibility to enzymatic degradation and short half-lives limit the therapeutic efficacy of these peptides in vivo [43]. To overcome these limitations, the mirror-image phage display technology has been developed [106]. This innovative approach focuses on identifying peptides composed of D-amino acids, which are more resistant to enzymatic degradation in the body compared to the conventional L-amino acid peptides. This resistance reduces unwanted immune responses, prolongs the peptides' half-life in circulation, and enhances their bioavailability, ultimately increasing their effectiveness [107-109]. In mirror-image phage display (as shown in Figure 1), the target molecule is synthesized using D-amino acids. Phage display is then employed to screen L-peptides that bind to the D-form of the target molecule. The identified L-peptide is subsequently synthesized using D-amino acids to create a D-peptide, which is expected to bind to the natural L-form of the target molecule, thus enhancing its therapeutic applications [110].

Wiesehan et al. using mirror-image phage display, identified a D-peptide inhibitor called D1 or D-pep with the sequence QSHYRHISPAQV. This peptide was recognized as a suitable target ligand due to its resistance to proteases and lack of unwanted immune responses. Studies showed that this peptide not only binds specifically to Aβ plaques but also reduces Aβ aggregation, demonstrating high potential for AD diagnosis and treatment [65]. van Groen et al. also used this technique to identify another D-peptide, D3 (RPRTRLHTHRNR), which specifically binds to Aβ42 [67]. Results revealed that D3 inhibited Aβ aggregation and converted toxic oligomers into non-toxic aggregates. Pharmacokinetic studies indicated that D3 has high proteolytic stability and can effectively increase brain penetration [67]. Based on these findings, several derivatives of D3, including D3D3, RD2 and RD2D3, have been developed, all of which demonstrated superior efficacy in removing toxic Aβ oligomers compared to D3. Pharmacokinetic studies of these peptides showed that all compounds crossed the BBB effectively, exhibited long half-lives, and demonstrated good accumulation in the brain [111-114].

Wang et al. synthesized a linear peptide with the sequence PYRWQLWWHNWS, based on screening a random 12-mer peptide library against Aβ1–10 [48]. This peptide was capable of specifically binding to Aβ1–10, inhibiting Aβ aggregation into plaques, and reducing Aβ-induced apoptosis. Additionally, it showed protective effects against Aβ-induced memory and learning deficits in animal models [87]. Larbanoix et al. utilized phage display to discover a six-amino acid linear peptide that prevents Aβ aggregation [63]. Two selected peptides, Pep1 (LIAIMA) and Pep2 (IFALMG), showed the highest binding affinity to Aβ1–42 with micromolar Kd values. In vitro studies demonstrated that these peptides did not exhibit specific toxicity toward neurons and thioflavin T aggregation assays confirmed that the designed peptides inhibited amyloid fibril formation [63].

Kawasaki et al. designed a random seven-amino acid (XX–P–XXXX) peptide library on the T7 phage based on the LPFFD sequence, where P stands for proline and X represents any other amino acid. The RGPRGRV peptide was identified, which demonstrated the strongest affinity for Aβ and inhibited Aβ oligomer formation [46]. In subsequent studies, random libraries containing 3- and 4-amino acid peptides were created and evaluated to assess the effect of peptide length on inhibiting soluble oligomer formation. Results showed that 3-amino acid peptides, due to their smaller size, were not significantly effective in inhibiting oligomer formation, whereas a 4-amino acid peptide with the sequence RFRK, similar to the seven-amino acid RGPRGRV peptide, inhibited soluble oligomer formation [50].

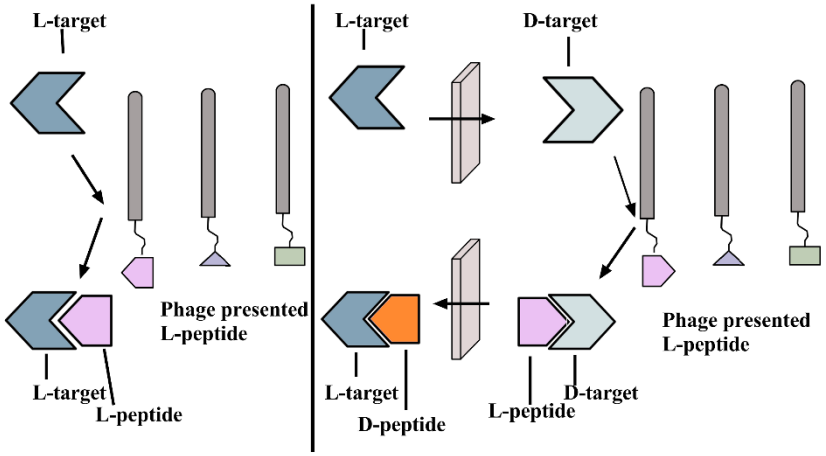

Figure 1. The schematic represents the phase display and the mirror image phage display

Aβ-inhibiting Peptides in Clinical Trials

In recent years, extensive research has been conducted on Aβ-inhibiting peptides in cellular and animal models aimed at developing novel therapeutic compounds to prevent Aβ aggregation. While these peptides have shown promising results in some studies, only a few have progressed to clinical trials. One such peptide, PPI-1019, commercially known as Apan, is an N-methylated peptide derived from the D-enantiomer of Cholyl-LVFFA-NH_2, designed to inhibit Aβ aggregation and toxicity. This peptide was optimized through structural modifications, including the replacement of the cholyl group with a methyl group and the substitution of the terminal D-alanine with D-leucine. PPI-1019 successfully completed phase I and phase II clinical trials in patients with mild to moderate AD, demonstrating safety, good tolerability, and the ability to cross the BBB (NCT00100282, NCT00100334). Although an increase in Aβ1-40 levels in cerebrospinal fluid was observed following administration, which may indicate enhanced clearance of Aβ from the brain, further clinical trials are needed to confirm its efficacy and evaluate long-term effects [31].

Currently, the peptide PRI-002 (also known as RD2), which is specifically being studied for its efficacy and impact on AD symptoms in patients with varying degrees of severity, is in Phase II clinical trials (NCT04711486). Initial results from this study are expected to provide valuable insights into the clinical effects and safety of this peptide and contribute to clarifying future prospects for the use of Aβ-inhibiting peptides in AD treatment. Other Aβ-inhibiting peptides, such as D3 [67], D-4F [115], TAT-RI-OR2 [116], and RI-OR2 [90], have shown significant efficacy in preclinical trials but have not yet advanced to clinical stages.

Conclusion

Peptide-based inhibitors represent a promising therapeutic strategy for AD, particularly due to their ability to target Aβ peptides, a key factor in the pathogenesis of AD. The specificity of these peptides for Aβ allows them to inhibit its aggregation into toxic oligomers and fibrils, which are directly linked to neurodegeneration. This review underscores the progress in the development of Aβ-inhibiting peptides, particularly those designed from the Aβ sequence itself, as well as those discovered through phage display and mirror-image phage display technologies. These peptides offer advantages such as high binding affinity, reduced neurotoxicity and the potential to improve brain penetration. Despite these advances, significant challenges remain. The rapid degradation of peptides by proteases, poor bioavailability, and difficulties crossing the BBB have limited their clinical application. Additionally, the tendency of these peptides to self-aggregate further reduces their therapeutic efficacy. However, innovative modifications such as the use of D-amino acids, cyclization and retro-inverso designs have improved peptide stability and therapeutic efficacy. These modifications enhance the pharmacokinetic profiles of peptides, making them more resistant to enzymatic degradation and improving their capacity to reach brain tissues. To develop more effective treatments, further research must focus on optimizing peptide design and understanding their molecular interactions with Aβ and other cellular components. Enhancing brain permeability and reducing self-aggregation are key fields for improvement. Combining rational design with advanced

delivery systems may enhance the chances of peptides advancing through clinical trials and contributing significantly to AD treatment. By addressing these challenges, we can unlock the full therapeutic potential of Aβ inhibitory peptides, offering hope for disease-modifying therapies in the future.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contribution's

Conceptualization, methodology, investigation, review and editing: All authors; Resources: Sajjad Molavipordanjani; Writing the original draft, supervision and funding acquisition: Solmaz Mojarad-Jabali;

Conflict of interest

The authors declared no conflict of interest.

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