

Peptoids: Emerging Therapeutics for Neurodegeneration

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ABSTRACT

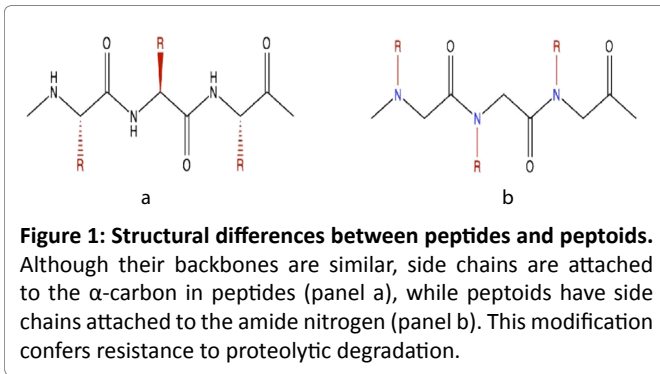
In recent decades, the increasing prevalence of age-associated neurodegenerative diseases has underscored the need for targeted therapeutic strategies and novel diagnostics. Peptide-based neurotherapeutics offer high specificity and tolerability but are limited by proteolytic degradation *in vivo*. Peptoids, or N-substituted glycines, are versatile peptidomimetics that evade proteolytic degradation yet maintain many qualities that render peptides attractive neurotherapeutic candidates. These molecules may be engineered to their application through modifications that enhance structural stability and reactivity and can withstand various physiological stressors to retain their intended function within anomalous microenvironments.

Peptoids generally demonstrate greater cellular permeability than their corresponding peptides, are less immunogenic, and can be administered intranasally, all properties that enhance their potential as neurotherapeutics. Peptoids have primarily been explored as aggregation inhibitors to prevent the deleterious protein plaque deposition associated with several neurodegenerative disorders. However, novel research has uncovered the potential of peptoids toward additional neurotherapeutic applications. Peptoids can modulate cell signaling pathways involved in axonal function and current modulation and can block cell signaling events associated with apoptosis. In addition, these peptidomimetics are able to function as anti-inflammatory agents via multiple mechanisms. Moreover, the versatility and low cost of peptoids render them ideal instruments in biomarker detection, discovery, and imaging. This mini-review explores these diverse applications of peptoids within the context of neurodegenerative disease.

Introduction

The increasing prevalence of neurodegenerative diseases that accompany an aging population, such as Alzheimer's disease (AD), Huntington's disease (HD), and Parkinson's disease (PD), underscores a need for effective therapeutic strategies. An improved understanding of the functional relevance of protein-protein interactions in homeostasis and disease pathologies has boosted the value of peptides as neurotherapeutic agents¹⁻³. Peptides can be synthesized to achieve binding specificity similar to native proteins, making them favorable for therapeutic strategies that disrupt or replace protein-protein interactions as well as broader applications, such as subcellular targeting strategies and detection of biomarkers for central nervous system (CNS) pathologies^{4,5}. Nonetheless, the practical application of peptide therapeutics *in vivo* is limited by vulnerability to proteases. While structural alterations can be introduced to increase peptide half-life, including D-amino acid substitution⁶, terminal acetylation or amidation⁷, and modification of the proteolytic site⁸, these alterations often reduce therapeutic activity⁶⁻⁸.

Peptoids, or oligomers of N-substituted glycines, are peptidomimetics that evade proteolytic degradation via repositioning of the side-chain from the α -carbon to the amide nitrogen (Figure 1)⁹. Peptoids are synthesized with relative ease and at comparatively low cost^{10,11}. While peptoids can be constructed to



mimic peptides in side-chain chemistry, a direct sequence translation is not always the most effective approach. Instead, the versatility of peptoids is often exploited through design, such as the incorporation of reactive sites or the conferment of structural stability through inclusion of chiral, aromatic side chains or cyclization of the peptoid^{9,12-15}. Peptoids exhibit increased cellular permeability as compared to the corresponding peptide, thus enhancing the potential for intracellular targets. Intranasal administration of peptoids also achieves effective delivery to the CNS, enabling use as a therapeutic for neurodegenerative diseases¹⁶⁻¹⁸. Additionally, peptoids are less likely than peptides to elicit an immunogenic response while retaining the ability to specifically target and inhibit protein-protein interactions^{19,20}. Together, these characteristics render peptoids an attractive, novel neurotherapeutic agent.

Peptoids as Aggregation Inhibitors

Several neurodegenerative diseases are amyloidoses, wherein a harmless protein monomer self-assembles to form toxic aggregates that possess a highly-ordered cross- β structure²¹⁻²³. AD, HD, and PD are neurodegenerative amyloidoses associated with aggregation of amyloid- β ($A\beta$), Huntingtin, and α -synuclein proteins, respectively. Pancreatic amylin amyloid is a common disorder in Type II diabetes; however, increased amylin amyloid has also been detected in the cerebrovasculature of late-onset AD patients who lack diagnoses for clinical diabetes^{21,23}. One therapeutic strategy for neurodegenerative amyloidoses is inhibition of aggregation or aggregate destabilization. Several peptoids have been explored as therapeutic agents toward this approach.

Starting from an on-bead library of more than 38,000 unique peptoid sequences containing four variable residues, Luo et al. identified a peptoid selective for $A\beta_{1-42}$, the more aggregation-prone form of the AD-associated amyloidogenic protein. Both the monomer and dimer of this peptoid inhibit $A\beta_{1-42}$ aggregation in a concentration-dependent manner. Moreover, the dimer demonstrates high affinity for $A\beta_{1-42}$ and also confers neuroprotection in an amyloid toxicity assay²⁴. A distinct anti-amyloidogenic peptoid also exhibiting high affinity for $A\beta_{1-42}$ was identified via surface plasmon resonance from a library of more than 4,000 six-mer peptoids containing four variable residues. This peptoid inhibits both early stage oligomerization as well as the formation of mature aggregates and protects against $A\beta$ -induced toxicity²⁵. Through rational design, an eight-mer peptoid was developed to both mimic the five-residue hydrophobic core of $A\beta$ and incorporate additional aromatic residues. This peptoid significantly attenuates the formation of fibrillar $A\beta_{1-40}$, the most abundant form of the AD-associated amyloidogenic protein²⁴. A subsequent study used variants of this

peptoid to examine the importance of side-chain placement and side-chain chirality on inhibition of $A\beta_{1-40}$ aggregation. Although both variants significantly reduce $A\beta_{1-40}$ aggregation, the absence of side-chain chirality leads to changes in the size and morphology of the aggregates formed, which have the potential to modulate aggregate toxicity^{13,26}. Two peptide-peptoid hybrids, designed to both mimic the $A\beta$ hydrophobic core and incorporate N-terminal hydrogen bond donors, also inhibit aggregation of $A\beta_{1-42}$ in a manner superior to their peptide counterparts. These peptide-peptoid hybrids additionally demonstrate stability in cell culture and attenuate $A\beta$ toxicity²⁷.

While inhibition of $A\beta$ aggregation by peptoids has been the most widely studied among neurodegenerative amyloidogenic proteins, peptoid inhibitors have also been explored within other amyloid-associated disease models. Chen et al. identified a peptoid that significantly inhibits aggregation of mutant polyglutamine-expanded Huntingtin fragments (mHtt). Intracerebroventricular infusion of the peptoid for 30 days reduced mHtt aggregate formation, stabilized Ca^{2+} signaling, and reduced neuronal apoptosis in a mouse model of HD²⁸. In a study targeting amyloid formation by amylin, a rationally-designed peptoid was developed to mimic amylin residues 20-29. This peptoid inhibits aggregation of the native amylin fragment *in vitro*²⁹. Overall, it is interesting to note that each of the peptoids reported to inhibit amyloid protein aggregation contains aromatic side chains, suggesting the importance of this structural element within the recognition and disruption processes.

Peptoids as Effectors of Cell Signaling

The intervention and modulation of cell signaling pathways offers an additional approach to CNS therapeutic development through disruption of deleterious signaling events. Protein-protein interactions that drive these pathways are potential therapeutic targets, and peptoids as well as peptide-peptoid hybrids have been explored as effectors of these interactions^{4,30}. A peptoid capable of modulating semaphorin 3A (Sema3A), a negative regulator of axon guidance that is overexpressed following CNS injury, was developed to promote axonal regeneration and reduce neural scarring. By blocking the interaction between glycosaminoglycans and Sema3A to attenuate Sema3A activity, this peptoid enhances neuronal regrowth *in vitro*³¹⁻³³. Therapeutic inhibition of histone deacetylase-6 (HDAC6) presents promise for neurodegenerative diseases, as evidenced by observations that HDAC6 inhibition rescues impaired axonal transport and HDAC6 knockdown improves function in a mouse model of AD^{34,35}. A recent study used rational design to identify a peptoid-based inhibitor of HDAC6. Although not yet investigated in neurodegeneration, this inhibitor is an effective chemosensitizing agent, a function for which HDAC6 has also emerged as a therapeutic target³⁶. Peptide-peptoid hybrids were investigated as potential antagonists for neurotensin receptor 2, a key receptor in the regulation of tonic pain sensitivity and some psychiatric diseases. The hybrids demonstrate a higher affinity for the receptor and inhibit constitutive mitogen-activated protein kinase (MAPK) activity stronger than the natural ligand neurotensin³⁷. Peptide-peptoid hybrid analogs of KIIIA, an endogenous voltage-gated sodium channel blocker, were developed to maintain high binding affinity but reduce the current blocked, thus providing a greater margin of safety for use as an analgesic. An N-methylglycine point substitution successfully lowers the blockage of current by 20%, creating a peptide-peptoid hybrid with more desirable functionality than naturally occurring KIIIA³⁸. Although direct

applications to neurodegeneration remain to be extensively explored, peptoids are well-established as effective modulators of cell signaling within the CNS thus exemplifying their potential in this capacity toward therapies involving neurodegenerative diseases.

Peptoids as Neuroprotective Agents

By targeting apoptotic signaling pathways, peptoids may also protect against neuronal loss. Two trialkylglycine peptoids confer neuroprotection against excitotoxicity-induced apoptosis, a common element in neurodegenerative pathogenesis. This protection correlates with diminished activation of caspase-3 without compromising N-methyl D-aspartate (NMDA) receptor activity, thus circumventing deleterious side effects of current drugs³⁹. Peptoids have also been used as antagonists for apoptotic protease-activating factor-1 (Apaf-1) to render the apoptosome complex inactive^{40,41}. Such antagonism impairs mitochondrial-mediated apoptosis, which is associated with many neurodegenerative diseases⁴². Introducing conformational constraint⁴³ and conjugation of the peptoid to cell penetrating peptides⁴⁴ or a polymeric carrier⁴⁵ enhance the effectiveness of these peptoids. Thus, peptoids can target neuroprotective pathways relevant to neurodegenerative diseases.

Peptoids for Attenuation of Neuroinflammation

Inflammation plays an active role in the development and progression of neurodegeneration, and suppression of neuroinflammation has become a target for therapeutic development^{46,47}. Peptoids have been proposed as an avenue for manipulation of antigen-specific immune responses by functioning as “antigen surrogates” to amplify a weak immune response or weaken a deleterious immune response through competition. Peptoids that incorporate backbone chirality to restrict conformation have been selected for high binding affinity

and selectivity to the antigen-binding site of therapeutically relevant antibodies, demonstrating the feasibility of this approach⁴⁸. In a different approach, peptoid mimics of catalase and superoxide dismutase have been designed to mitigate the impact of oxidative stress, an integral component of inflammation. These peptoids bind redox-active metal ions to form complexes capable of scavenging and detoxifying reactive oxygen and nitrogen species^{49,50}. To modulate activation of immune cells, lipidated peptide-peptoid hybrids have been identified as both agonists⁵¹ and antagonists^{52,53} of formyl peptide receptor 2 (FRP2), expressed by neutrophils and involved in neutrophil activation. Upon binding FRP2, antagonists are able to attenuate FRP2-specific activation of neutrophils^{52,53}. These examples demonstrate that peptoids hold promise for attenuating neurodegeneration-associated inflammation via a variety of mechanisms.

Peptoids for Biomarker Detection and Imaging

The symptomatic and pathological overlap across many neurodegenerative diseases complicates their diagnosis, and the inaccessibility and complexity of the CNS present challenges for diagnostic assays⁵⁴. When coupled with the difficulty of reversing neuronal damage, which implicates early intervention as a key to successful therapeutics, these circumstances underscore the need for novel biomarker discovery and diagnostic tools. Through their specificity and stability, relatively low cost, and ease of modification, peptoids may function as biomimetic receptors with diagnostic applications^{4,5,12,55}.

A combinatorial library of peptoids can be readily created to provide a random, diverse set of molecules from which to select a capture agent for biomarkers within an accessible biological fluid. This approach has been used to discover a peptoid ligand with nanomolar binding affinity that is selective for Aβ₁₋₄₂ (vs. Aβ₁₋₄₀), a suggested biomarker for AD²⁴. By applying a peptoid

Binding Target	Intervention	Source(s)
Amylin	Inhibition of aggregation	29
Aβ ₁₋₄₀	Inhibition of aggregation	13
Aβ ₁₋₄₂	Inhibition of aggregation; Inhibition of Aβ neurotoxicity	24, 25
Aβ ₁₋₄₂	Peptide-peptoid hybrid; Inhibition of aggregation; Inhibition of Aβ neurotoxicity	27
Apaf-1	Neuroprotection via inhibition of mitochondrial-mediated apoptosis	40, 41, 44, 45
Apaf-1	Inhibition of apoptosome formation	43
Oxidative stress by-products	Catalase and superoxide dismutase mimic; Neutralization of reactive oxygen and nitrogen species	49, 50
FRP2	Peptide-peptoid hybrid; Receptor antagonist; Attenuation of neutrophil activation	51– 53
HDAC6	Inhibition of HDAC6 enzymatic activity	36
mHtt	Inhibition of aggregation; Protection against neurotoxicity; Stabilization of Ca ²⁺ signaling	28
IgG antibodies	Biomarker detection	58, 59
Voltage-gated sodium channels	Peptide-peptoid hybrid; Blockage of current	38
NTS2	Peptide-peptoid hybrid; Receptor antagonist; Inhibition of MAPK enzymatic activity	37
Sema3A	Promotion of axonal regrowth	31, 33
Unknown	Neuroprotection correlated with reduced caspase 3 activity	39
VEGF receptor 2	In vivo imaging	60

Table 1: Prospective neurotherapeutic applications of peptoids and peptide-peptoid hybrids.

library to compare antibody capture between patient and control samples, an antibody-peptoid ligand set can also be identified without prior knowledge of the antibody biomarker itself. Such a strategy offers a distinct advantage for many neurodegenerative diseases wherein effective biomarkers have not been identified and antibodies are suggested as prospective biomarker candidates^{56,57}. In this manner, potential IgG antibody biomarkers have been discovered within an animal model of multiple sclerosis and human subjects with AD⁵⁸ and PD⁵⁹. Peptoids may also be leveraged for imaging applications to add specificity to contrast and imaging agents. A potent peptoid antagonist for vascular endothelial growth factor (VEGF) receptor 2 was labeled with a positron emitter for successful positron emission tomography (PET) imaging of the receptor *in vivo*⁶⁰. While Hao et al. applied this technology for tumor imaging, parallel approaches could be developed using peptoid ligands for neurodegeneration biomarkers, which may range from altered receptor expression to amyloid deposition.

Conclusion and Future Perspectives

Peptoids were first proposed in 1992 with the original intent of advancing the drug discovery process⁹. These molecules offer a great deal of potential as therapeutics for neurodegeneration and for applications beyond this sphere. Already, peptoids have been explored as agents for anti-aggregation, neuroprotection, anti-inflammation, biomarker detection and discovery, and imaging, as summarized in Table 1. Their stability, specificity, and enhanced permeability equip peptoids with the therapeutic advantages of both small molecules and peptides. Subcellular targeting facilitates treatment, and structural stability allows peptoid functionality to be retained in extreme physiological environments. For example, β -secretase, the rate-limiting enzyme in A β release from its protein precursor, is activated within the acidic climate of early endosomes; peptoids exemplify β -secretase inhibitor candidates with the potential for both targeted delivery to this compartment and stability within this environment⁴. Their size and capacity for intranasal delivery also make peptoids a compelling prospect for neurological interventions¹⁶⁻¹⁸. In addition to their many current potential applications, the possibilities for these degradation-resistant protein-mimetics grow with increased knowledge of peptoid assembly and folding behavior.

Conflict of Interest

The authors report no competing interests.

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