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From Nose to Brain: The Promise of Peptide Therapy for Alzheimer's Disease and Other Neurodegenerative Diseases

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Abstract

The pathological hallmarks of Alzheimer's disease (AD) are the deposition of extracellular senile plaques resulting from amyloid-β (Aβ) peptide aggregation, the formation of intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, and extensive neuron death. Although 110 years have passed since the discovery of AD, the field still debates whether the amyloid hypothesis or tau hypothesis is the key issue in AD therapy. The issue of population aging makes the prevention or therapy of AD a pressing issue since the onset of this disease is highly age-correlated. Over the past two decades, the number of AD-related publications per year has grown rapidly, but to no avail. The failure rate of anti-AD clinical trials is ~99.9% and only cholinergic drugs for symptomatic control are available in the market. The success of the phase 1b clinical trial of Aducanumab immunotherapy in 2014 rekindled interest in anti-amyloid therapy, whereas the failure of the phase 3 clinical trial of Solanezumab immunotherapy once again quashed the optimism.

Recently, a peptide therapy for AD was developed. A polyethylenimine (PEI) conjugated peptide, V24P(10-40)-PEI, was proposed to serve as a scavenger by trapping endogenous Aβ produced in the brain to avoid the formation of toxic aggregates. Most importantly, this peptide was given as a nose drop. After treating the AD double transgenic mice APP/PS1 with V24P(10-40)-PEI for four months, there was a significant reduction in Aβ accumulation in the brains of the treated mice. V24P(10-40)-PEI was designed to trap Aβ to interfere with its self-association, which renders Aβ more vulnerable to the attack of various endogenous Aβ-degrading enzymes.

Keywords: Peptide; Alzheimer's disease; Intranasal

Peptides designed to inhibit Aβ amyloid formation

Many mutations affecting Aβ production or accelerating Aβ aggregation result in early-onset familial AD [1,2], and there is an APP mutation nears the β-cleavage site that protects against the development of late-onset dementia [3]; this evidence strongly supports the amyloid cascade hypothesis. Moreover, Aβ deposition might start ~20 years before expected symptom onset in familial AD [4], suggesting the importance of anti-amyloidopathy in AD prevention. Thus, many peptides have been designed to inhibit Aβ amyloid formation. Most of the peptide inhibitors were designed based on the Aβ sequence [5-14] and some of them were obtained from random screening [15-18]. These peptides were selected based on their ability to inhibit Aβ fibrillization and to reduce Aβ-induced toxicity. However, very few have been tested *in vivo* (Table 1). The *in vitro* efficacy in inhibiting the toxicity and amyloid fibril formation of Aβ does not guarantee the success of this peptide in reducing amyloid plaque accumulation in the brain, as shown in the case of the D1 peptide [17].

Peptide drug delivery is a key issue

Peptide therapy hinges on peptide stability and delivery. How can we prolong the lifespan of these peptides in the body? How can they pass the blood-brain barrier into the brain? Juhasz et al. intravenously injected tritium-labeled pentapeptide, which has sequence LPYFD and C-terminal amidation, in rats to study its biodistribution. The majority of the radioactivity was detected in the liver, followed by the kidney and the stomach, with only ~0.3% detected in the brain [19]. Therefore, most anti-AD peptide drugs are tested in animals either by intraperitoneal injection or intracerebral infusion [12,17,18,20-22]. From the prevention point of view, neither intraperitoneal injection nor intracerebral infusion is practical. Another method, oral feeding, has only been tested for the peptide D3, which is composed solely of D-amino acids [23]. Although positive responses were obtained in amyloid deposition and cognitive behavior, the oral dosage of D3 is huge (0.5-1 mg/mouse/day).

To increase brain targeting, intranasal delivery is an excellent non-invasive form of administration [24]. Banks et al. reported that, compared with intravenous administration, intranasal administration of radioactively labeled exendin(9-39), a glucagon-like peptide-1 (GLP-1) receptor antagonist, was four times more effective in delivery to the olfactory bulb, but three times lower in delivery to the rest of the brain [25]. Except for the olfactory bulb, there was no statistically significant distribution difference in the different brain regions. The amount of radioactively labeled exendin(9-39) in the brain via the intranasal route is less than 0.3% of the administrated dose per gram of tissue. The success of V24P(10-40)-PEI proved intranasal administration combined with PEI conjugation to be a feasible design to efficiently deliver peptides into the brain. Using fluorescence-labeled R_8-Aβ(25-35)-PEI peptide, more than 17% of this peptide can be transported from the nose to the brain, reaching a maximum peptide level in the brain after 6 h [26]. A similar study also intranasally delivered the peptide wtNBD to AD transgenic mice [27]. wtNBD does not have PEI conjugation, but contains a cell-penetrating peptide segment with many positively charged residues. The data from these peptides suggest that the poly-positively charged moiety can help the peptides move from the olfactory epithelium in the nasal

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Peptide	Sequence	Proposed mechanism	Animal data	Delivery
V24P(10-40)-PEI [1]	Ac-YEVHHQKLVFFAEDpGSNKGAIIGLMVGGVV-PEI (31 a.a.)	trap Aβ to avoid its self-aggregation	Aβ↓	intranasal drop
R_8-Aβ(25-35)-PEI [26]	Ac-RRRRRRRRGSNKGAIIGLM-PEI (19 a.a.)	inhibit Aβ fibrillization	Aβ↓ inflammation↓ memory↑	intranasal drop
wtNBD [27]	DRQIKIWFQNRRMKWKKLDWSWL (23 a.a.)	inhibit NF-κB activation	Aβ↓ inflammation↓ memory↑	intranasal drop
TFP5 [22]	FITC-GGGKEAFWDRCLSVINLMSSKMLQINAYARAARRAARR (38 a.a.)	inhibit Cdk5 activation	Aβ↓ p-tau↓ inflammation↓ apoptosis↓ memory↑	IP injection
iAβ5p [12,20]	Ac-LPFFD-NH_2 (5 a.a.)	inhibit Aβ fibrillization; disaggregate Aβ fibrils	Aβ↓	IP injection ICV infusion
D3 [17,21]	rprtrlhthrnr (12 a.a.)	bind Aβ42; inhibit Aβ fibrillization	Aβ↓ Microglial↓ GFAP↓	IH infusion;
D3 [23]	rprtrlhthrnr (12 a.a.)	bind Aβ42; inhibit Aβ fibrillization	Aβ↓ memory↑	oral
D-Trp-Aib [18]	w-Aib (2 a.a.)	inhibit Aβ oligomerization	Aβ↓ memory↑.	IP injection
NAP [29,30]	NAPVSIPQ (8 a.a.)	promote microtubule assembly	Aβ↓ p-tau↓ memory↑	intranasal drop
PACAP38 [31]	HSDGIFTDSYSRYRKQMAVKKYLAAVLGKRYKQRVKNK (38 a.a.)	anti-inflammatory; neuroprotective	α-secretase↑ novel object recognition↑	intranasal drop

Ac: Acetylation; NH_2: Amidation; PEI: Polyethylenimine; FITC: Fluorescein Isothiocyanate; Aib: α-Aminoisobutyric Acid; GFAP: *Glial Fibrillary Acidic Protein*; IP: Intraperitoneal; ICV: Intracerebroventrical; IH: Intrahippocampal

Table 1: Peptide drugs that have been tested in AD animal models. D-amino acids are represented by the lowercase single letter code of L-amino acids. Peptide modifications are highlighted in grey.

cavity to the brain. PEI is a polycationic polyamine with a branched backbone and has long been used in assisting DNA transfection across the cell membrane. Compared to the poly-positively charged peptide sequence, PEI has a higher charge-to-mass ratio than poly-Arg or poly-Lys. It can easily be coupled to the carboxyl group of the C-terminus of peptides, and this conjugation can protect peptides from exopeptidase attack to extend the half-life. Moreover, because PEI can carry large proteins such as green fluorescence protein from the nose to the brain [28], PEI-conjugation can potentially transport the functional proteins that are beneficial for brain functions, such as brain-derived neurotrophic factor and insulin, into the brain.

Other designed anti-AD peptides

Many peptides designed to work on other pathways also showed efficacy against amyloidopathy. For example, the peptide wtNBD was designed to inhibit the induction of NF-κB activation, not to directly target Aβ. Giving wtNBD to the 5XFAD mice via intranasal administration for 30 days suppresses microglial activation, reduces Aβ plaque deposition, and improves the cognitive performance of the mice [27]. TFP5 contains a fluorescence tag, a truncated fragment of p35, which is an activator of cyclin-dependent kinase 5 (Cdk5), and a segment derived from Tat protein (with many Arg residues) for cell penetration. Cdk5 is hyperactivated in AD brains. The complex formed of Cdk5 and p25, a proteolytic product of p35, can cause the aberrant hyperphosphorylation of tau and neurofilaments and has been identified as a therapeutic target for AD. TFP5 was designed to inhibit Cdk5/p25 activity and tau hyperphosphorylation, yet its administration to the 5XFAD mice by intraperitoneal (IP) injection not only reduced the phosphorylation of tau and neurofilaments, but also decreased Aβ accumulation and neuroinflammation in the brains of these mice [22]. Intranasally administered NAP, an octapeptide promoting microtubule assembly, reduced both Aβ accumulation and tau hyperphosphorylation in the 3xTg AD mice [29,30]. Amyloidopathy and tauopathy might be more complicated and correlated than previously thought. Pituitary adenylate cyclase-activating polypeptide (PACAP)38 has an anti-inflammatory and neuroprotective peptide. Daily intranasal treatment of PACAP38 in the APP_{V717I} transgenic mice for three months increased α-secretase activity and improved cognitive function [31]. Therefore, a "multi-target" therapy potentiates an additive effect in AD prevention. Recently, several peptides were designed to inhibit tau aggregation based on the VQIVYK sequence, which is adopted from the human tau sequence 306-311 and is the crucial segment in the fibril formation of tau. One D-peptide, with the sequence TLKIVW, was designed based on computer modeling [32]. Several 12-mer D-peptides were screened from a peptide library using the mirror image phase display technique [33]. These anti-tau peptides are protease resistant, as they are composed only of D-amino acids, but have not yet been tested on animal models. The evidence indicates the value of testing PEI-conjugated anti-tau peptides delivered intranasally. Moreover, a "peptide cocktail" with multiple targets may be the most promising strategy.

Conclusion

The success and failure of anti-Aβ immunotherapy demonstrated the need to prevent AD from a very early stage. Furthermore, the prolonged nature of AD progression implies that prevention is a long battle too. The goal is convenient treatment without side-effects-criteria that match intranasally delivered peptide therapy. Although the design of these intranasal anti-AD peptides does give them the ability to target specific anatomic regions in the brain, the animal results showed that they can function in the places where they are needed [1,26,27,29,30]. Moreover, the misfolded protein aggregates found in other neurodegenerative diseases such as Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and prion diseases suggests a broad application for peptide therapy in the future.

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