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Mirror image supramolecular helical tapes formed by the enantiomeric-depsipeptide derivatives of the amyloidogenic peptide amylin(20–29)

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Abstract

Factors that determine the chirality of supramolecular helical tapes formed by a backbone-modified amylin(20–29) depsipeptide and inverso-depsipeptide, were studied by Fourier transform infrared spectroscopy, circular dichroism and transmission electron microscopy. Although β-sheet propensity was absent in both peptides, it was found that the L-depsipeptide formed left-handed and the enantiomeric D-depsipeptide right-handed helical tapes. Moreover, the backbone-modified depsipeptides, showed a certain degree of cross-recognition between both enantiomers, which might have implications in designing amyloid formation inhibitors.

Keywords: Amyloid; Depsipeptide; Peptide nanotubes; Self-assembly; Soft matter

Amyloid formation is the most prominent example of protein self-assembly and represents a self-propagating process responsible for the formation of supramolecular assemblies like amyloid fibrils, amyloidogenic plaques, and proteinaceous aggregates.[1] Amylin consisting of 37 amino acid residues is a highly amyloidogenic peptide and is involved in type 2 diabetes (late onset diabetes) since fibrillar deposits of amylin are cytotoxic for β-cells and subsequently responsible for insulin insufficiency.[2] The sequence of amino acid residues 20–29: Ser-Asn-Asn-Phe-Gly-Ala-Ile-Leu-Ser-Ser **1** (Fig. 1) is recognized as the most amyloidogenic sequence within amylin[3] and rapidly forms amyloid fibrils.

Based on this sequence, we have designed depsipeptide **2** as a potential β-sheet breaker peptide, since the essential amide bonds involved in β-sheet formation have been replaced by ester moieties to disrupt the hydrogen bonding network of the antiparallel β-sheet.[4] However, it turned out that depsipeptide **2** was substantially less potent as a β-sheet breaker than expected since this peptide gave rise to self-assembly leading to helical tapes and peptide nanotubes. Structural investigations by FTIR (Table 1) and CD spectroscopy (Fig. 2) showed that the characteristic properties of a β-sheet secondary structure were absent in the case of depsipeptide **2**. Based on these data it was concluded that the increased hydrophobicity and intrinsic chirality of the depsipeptide were responsible for the self-assembly into helical tapes rather than a hydrogen bond driven process.[4]

In the recent literature, several reports describe the transformation of the molecular chirality of a peptide into the handedness or twist of a supramolecular construct.[5] Peptides, which have a propensity to β-sheet formation, self-assemble into diverse types of twisted morphologies

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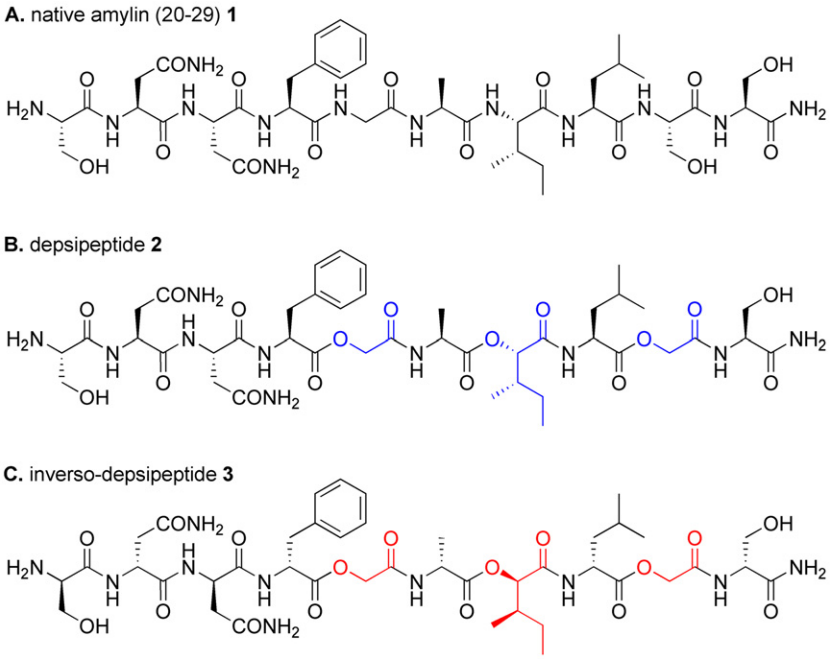

Fig. 1. Structures of native amylin(20–29) (**1**) and the corresponding depsipeptide (**2**) and inverso-depsipeptide (**3**).

Table 1
Physicochemical properties of the amylin(20–29) derivatives

Compound	R_t (min)	ESMS $[M+H]^+$ found (calcd)	FTIR[a] (cm^{-1})	Morphology[b]
1[4,13]	17.15	1008.65 (1008.50)	1631 (s)	Typical amyloid fibrils
L-Depsipeptide **2**	17.57	981.45 (981.45)	1663 (s)	Left-handed helical tapes
			1640 (m)	Helical tapes progressing into tubes
			1740 (w)	
D-Depsipeptide **3**	17.60	981.45 (981.45)	1663 (s)	Right-handed helical tapes
		$[M+Na]^+$ 1002.75	1640 (m)	Closed tubes
			1739 (w)	
2 + **3** (1:1 w/w)	—	—	—	Flat ribbons

[a] Typical amide I absorption frequency (cm^{-1}), 1630: aggregated β-sheets; 1640: unordered structure; 1675: antiparallel β-sheet; 1740 carbonyl in ester bond, according to Ref. 14.
[b] As observed by TEM.

such as helical tapes, twisted ribbons, fibrils, and fibers.[6,7] The twist supposedly stems from the intrinsic chirality of the L-amino acid building blocks of the peptide. Theoretical studies on the origin of β-sheet twisting demonstrate the right-handed twist of a β-strand,[8] which gives rise to a left-handed twist around the long axis of the tape.[6]

To obtain more insight into the self-assembly of depsipeptide **2**, and especially with respect to the handedness of a supramolecular helical tapes, the enantiomer of **2**, inverso-depsipeptide **3**, was synthesized. The synthesis of **3** started with the conversion of (2*R*,3*R*)-2-amino-3-methylpentanoic acid (D-isoleucine, **4**) into its corresponding α-hydroxy derivative (H-Ilec-OH) in the presence of $NaNO_2/H_2SO_4$ according to the procedure described by Shin et al.[9] followed by the esterification with allylbromide/K_2CO_3 to give α-hydroxy ester **5**[10] in 54% overall yield (Scheme 1). Then, Fmoc-D-Ala-OH was coupled with DCC/DMAP as coupling reagents and the protected depsidipeptide was obtained in 70% yield. Finally, the allyl group was removed by treatment with $Pd(PPh_3)_4$/phenylsilane to give Fmoc-D-Ala-D-Ilec-OH (**6**)[11] in 95% yield. Building block **6** was used in the solid phase synthesis of inverso-depsipeptide **3**[12] analogously as previously described for its depsipeptide **2**.[4]

Native amylin(20–29) **1** was used as the reference peptide. A solution of **1** (10 mg/mL in 0.1% TFA/H_2O, pH 1) rapidly formed an opaque gel since gelation is an indication of peptide fibrillization at sufficiently high concentration. The formation of amyloid fibrils was verified by transmission electron microscopy (TEM),[4,13] FTIR (Table 1),[14] and CD spectroscopy (Fig. 2; Note: a peptide solution of 1 mg/mL in 0.1% TFA/H_2O, pH 1 was used for the CD measurements otherwise a turbid CD sample was obtained. Moreover, as a control, TEM- and FTIR studies verified the presence of amyloid fibrils at this peptide concentration (data not shown)). Depsipeptide **2** was dissolved in 0.1% TFA/H_2O (10 mg/mL, pH 1) and rapidly (within 10 min) gelled the solution upon standing at 4 °C. TEM studies