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Review article

Peptaibols as a model for the insertions of chemical modifications

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ABSTRACT

Peptaibols are linear non ribosomal peptides which have been the object of intense research efforts regarding their synthesis and the elucidation of the mechanism allowing their insertion in biological membranes. Forty years after their discovery they are still considered as model compounds and suitable probes for the investigation of new approaches aiming to test the efficacy of new coupling reagents, to physically and spectroscopically investigate the way by which they interact with the lipid bilayer and to develop artificial membrane pores. The stable helical secondary structure adopted by the peptaibols turn to be an adequate platform for gaining insight on the structural modifications induced by the substitution of the amide bond by 1,2,3-triazoles, but also for monitoring the impact of newly designed α,α-dialkyl glycine with fluorinated and silylated side chains as 2-aminoisobutyric acid mimic. Peptaibols secondary structure dictated by Aib high content has inspired the development of foldamers. Challenges and investigations on the above mentioned topics are discussed in this brief review.

1. Introduction

Peptaibols are a set of linear antibiotic peptides of length varying from 5 to 20 amino acids biosynthesized by fungus species of the genus *Trichoderma* [1]. The principal features of these peptides consist in a high occurrence of non-proteinogenic C-alpha tetrasubstituted amino acids such as the achiral alpha-aminoisobutyric acid (Aib) or the more rare isovaline (Iva) (Fig. 1A) [2]. Peptaibol N-terminal amino acid is generally acylated while the C-terminus is a β-amino alcohol, the phenylalaninol, leucinol, valinol and isoleucinol being the most frequent. Two data bases compiling the peptaibol sequences and the existing structural informations are freely available on the web [3,4]. Accordingly to their length, peptaibols are subdivided in three categories the long have a sequence of 18–20 amino acids, the medium are made of 12–16 amino acids and the short length are above 11 residues, peptaibolin (AcLeuAibLeuAibFol) being the shortest example of this last compound class with a three-dimensional structure available (Fig. 1) [5]. The most recent data base contains also the close related lipopeptaibols that differs by the presence of a fatty acyl moiety at the N-terminal amino acid [6,7]. Both compound classes are referred as peptaibiotic and the name of peptaibiomics was recently applied to the analysis of extracts from fungus producing them [8,9].

Since the discovery of alamethicin (Alm) in 1967 [13], the archetype of peptaibol [14,15], these compounds have raised considerable interest because of their peculiar conformation and have proven useful in studies directed towards the comprehension of helical structured peptide interactions with membranes [16]. Indeed, the non-ribosomal Aib has pronounced effect on the conformation of the peptide backbone which folds into amphiphilic 3_{10}- and α-helices as proven by the different structural analysis by means of CD spectroscopy, NMR and X-ray diffraction studies. Thus twenty three-dimensional structures of natural peptaibols have been reported which included peptaibols of various length such as peptaibolin, bergofungin A, zervamicin, and alamethicin (Fig. 1). Self-association of peptaibols form helical bundles into bilayer membranes leading to ion-pores [17] that cause cell lysis and account for their broad spectrum of biological activity targeting bacteria, fungi, parasites and mammalian cells such as cancer cells. The way peptaibols act on membrane was often compared with cationic antimicrobial peptides (AMP) as both of them are believed to form different pore types described as barrel-stave or toroidal pores, respectively. The pore formation was extensively studied using oriented circular dichoism, X-ray diffraction, scattering experiments and molecular dynamics simulation (Fig. 2) [18–20].

Alm was shown to be particularly useful in such studies and was qualified as "the simplest and most easily interpretable model for channel-forming, complex protein systems" in a review entitled "You are sitting on a gold mine" [22]. Thus peptaibols structure have inspired the synthesis of simplified non-natural analogues mimicking

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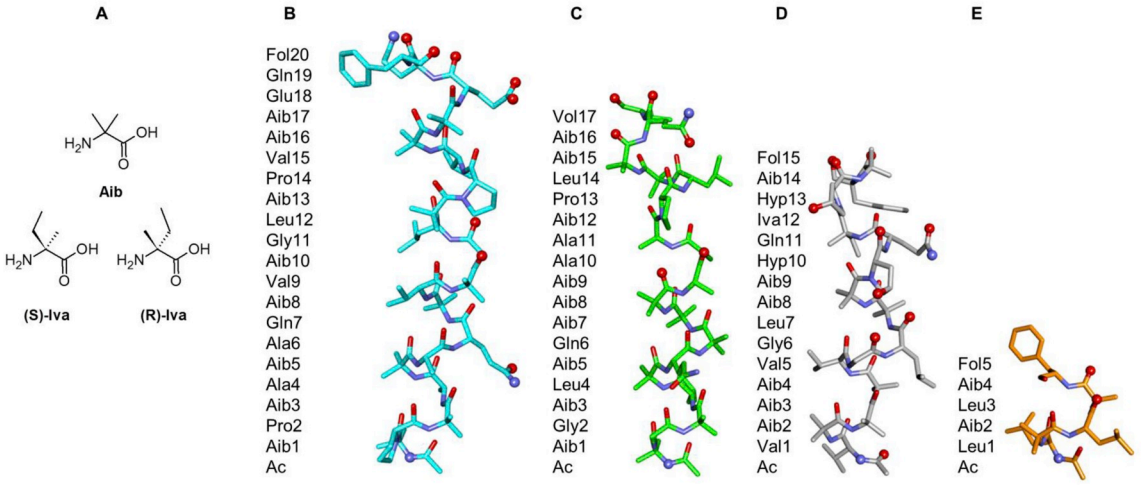

Fig. 1. A. Structure of amino-isobutyric acid (Aib) and of isovaline (Iva). Sequences and crystal structures of representative peptaibols with different length: B. Alamethicin (in cyan, PDB entry 1amt) [10], C. Trichotoxin (in green, PDB entry 1m24) [11], D. Bergofungin A (in grey, PDB entry 5mas) [12] and E. Peptaibolin (in orange, CDC entry 160328) [5]. Solvent accessible atoms constituting the polar face of the amphipathic helix are indicated as spheres. Ac: acetyl; Fol: Phenylalaninol; Vol: Valinol; Hyp: Hydroxyproline; Iva: Isovaline.

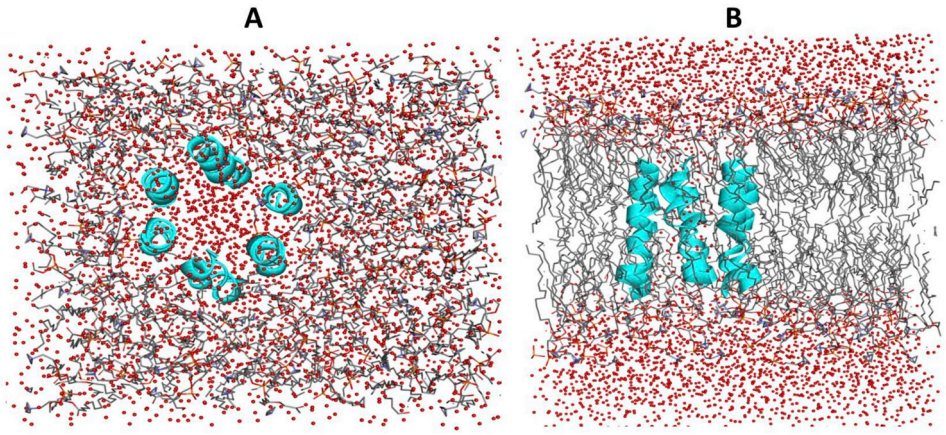

Fig. 2. Model of a channel formed into POPC (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine; grey sticks) artificial membranes by the self-association of six Alamethicin monomers (in cyan). A. Top view. B. side view of the water (red spheres) filled channel [21].

protein-like ion channels functions [23].

Peptaibols biological and physicochemical properties are closely related to the high proportion of Aib in their sequences. The gem-dimethyl substituents at the Aib C-α-atom induce preferred 3_{10}-helix for short peptaibol sequence, while α-helix is adopted for chain length above 15 residues. The specific structural properties of Aib have been discussed and are out of the scope of this review [22,24]. Reviews have been entirely devoted to the aspects concerning the biosynthesis, biological activity and conformation of peptaibiotics in special issues of Journal of Peptide Science, Chemistry and Biodiversity directed by researchers passionate by these compounds and therefore qualify as "peptaibomaniacs" [16,25–27].

In this review, we essentially discussed the chemical modifications of peptaibols by the introduction of tailor-made amino acids, thus punctual amino acid mutations when not associated with the purpose to confer new physicochemical properties have not been retained. Nevertheless, the contribution of new coupling reagents for an easier production of peptaibols by means of solid phase peptide synthesis will be examined. Indeed, improvement of their synthesis, their helical structures along with their biological properties has allowed to consider peptaibols as useful templates for the introduction of fluorine, and other spectroscopically actives probes for deciphering their biological mechanism of action on membranes. Peptaibols were also used as probes to monitor the introduction of silylated amino acids and to assess the consequences of the substitution of amide bound with the well-known 1,2,3-triazole mimic. Finally, this review will not be completed without bringing up shortly the influence of peptaibols in the development of foldamers that constitutes the last part of the article. The authors invested significant efforts to cover the whole of the literature published during the range 2010–2018 and will to apologize for any unintentional omission.

2. Solid phase peptide synthesis (SPPS) of peptaibols, a contribution to the development of new coupling reagents

Stepwise peptaibols SPPS was impaired by the low reactivity of the hindered Aib. Thus, solution synthesis by fragment condensation has long been the preferred route until the advent of efficient coupling reagents and/or microwave assisted synthesizers [28–32]. The flexible segment condensation approach developed by Peggion et al. [33] remain broadly used by researchers willing to synthesize newly isolated peptaibols [34], nevertheless solid phase peptide synthesis optimized protocols tend to appear as a suitable option.

As Aib is difficult to couple standard coupling reagents such as HBTU (2-(1*H*-1,2,3-benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate) cannot be used, and therefore chemist choose to