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LANTIBIOTICS - NOVEL ANTIBIOTICS

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Introduction

The spread of bacterial resistance leads to a growing demand for novel antibiotics. However, despite significant efforts in pharmaceutical industry, no genuinely new class of antibacterial compounds has reached the market for almost 20 years. Industrial strategies for searching for antibiotics with novel mechanisms of action include the screening of large 'libraries' of synthetic compounds for inhibitors of targets that have not yet been exploited in antibacterial chemotherapy. The advantage of this approach is that it leads to compounds of low molecular mass which are relatively easy to modify by medicinal chemistry. On the other hand, such 'hits' obtained from in vitro assays still have to overcome major obstacles, e.g. penetration into the intact bacterial cell, an appropriate antibacterial spectrum, favourable pharmacokinetics and low toxicity, before they can be marketed. Therefore, other approaches, such as a detailed evaluation of the potential of existing classes of antimicrobial compounds, are still valuable. Although many of these substances have been known for years, the molecular mechanisms by which they kill bacteria are sometimes poorly characterized. In some cases, a better understanding of this process may help to improve the utility of the class of agents. One example is the lantibiotics, where recent investigations into the molecular mechanism of action have led to unexpected results. It became evident that representatives of different classes of lantibiotics share the same molecular target although this interaction leads to different antibacterial effects. In one particular case, two different mechanisms of action appear to reside in the same molecule and these combine to produce high-potency antimicrobial activity.

History

The name lantibiotics was introduced in 1988 as an abbreviation for "lanthionine containing peptide antibiotics". The first structures of these antimicrobial agents were produced by pioneering work by Gross and Morell in the late 1960s and early 1970s, thus making the formal introduction of lantibiotics. Since then lantibiotics such as nisin have been used auspiciously for food preservation and have yet to encounter significant bacterial resistance. These attributes of lantibiotics have led to more detailed research into their structures and biosynthetic pathways. Lantibiotics are a class of peptide antibiotics that contain polycyclic thioether aminoacids as well as the unsaturated aminoacid dehydroalanine and 2- amino isobutyric acid. These characteristic cyclic thioether aminoacids are composed of either lanthionine or methyl lanthionine. Lantibiotics are produced by a large number of Gram positive bacteria such as Streptococcus and Streptomyces to attack other Gram positive bacteria.

Classification of Lantibiotics

Lantibiotics have since been identified and can be divided into two groups on the basis of their structures and designated as Type-A and Type-B

- Type A lantibiotics are long flexible molecules – e.g. nisin, subtilin, epidermin. Type A is divided into A I and A II. Subgroup A I includes mutacin II; Subgroup A II includes mutacin I and III.

- Type B lantibiotics are globular- e.g. mersacidin, actagardin, cinnamycin

Biosynthesis

Lantibiotics are a class of peptides produced by a range of Gram positive bacteria. Initially synthesised on ribosome as unmodified peptides including a leading sequence which is subsequently and proteolytically removed, these prepeptides undergo a series of modifications prior to conversion to their active form and transport from the cell.

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Table 1: Potential Biomedical Applications, Cotter et.a l (2005)

Lantibiotic	Producing strain	Inhibitory activity of commercial interest	Potential biomedical application
Nisin A	*Lactococcus lactis*	Gram positive bacteria, Gram negative bacteria including *Helicobacter pylori*	bacterial mastitis, oral hygiene, treatment of methicillin resistant *Staphylococcus aureus(M*RSA) and enterococcal infections, cosmetic deodorants and topical formulations, peptic ulcers, lung mucus clearing, treatment of enterocolitis
Lacticin 3147	*Lactococcus lactis*	Gram positive bacteria	bacterial mastitis, treatment of MRSA infections, enterococcal infections, oral hygiene
Gallidermin Epidermin	*Staphylococcus gallinarum* *Staphylococcus epidermidis*	*Propionibacterium acnes,* staphylococci and Streptococci	Acne,folliculitis,eczema,impetigo
Mutacin 1140	*Streptococcus mutans*	*Streptococcus mutans*	Prevention of dental caries
Mersacidin Actagardin	*Bacillus subsp. Actinoplane subsp.*	Staphylococcus including methicillin resistant strain, Streptococci	Treatment of MRSA and Streptococcal infections
Duramycin	*Streptomyces subsp. Streptoverticillum subsp.*	weak bacterial inhibition, phospholipase A2 inhibitor	Inflammation
Cinnamycin	*Sreptomyces cinamoneus*	inhibitor of phospholipase A2, angiotensin converting enzyme(ACE) and Herpes simplex virus	Inflammation, blood pressure regulation, viral infection treatment
Ancovenin	*Streptomyces subsp.*	Inhibitor of ACE	blood pressure regulation

Modification of prepeptide include the dehydration of specific serine and threonine residues; these residues then cross link with cysteine thiols forming the characteristic methyl lanthionine bridges which impart structural stability and reduced susceptibility to proteolytic attack. Additional modification includes deamination of dehydrated N terminal serine or threonine residues. The gene encoding the biosynthesis of lantibiotics are clustered and designated as 'lan'. Although the arrangement and number of genes vary between clusters, each contain (1) structural gene - lanA,which for the prepeptide (2) A single lanM gene or otherwise a lanB or lanC, the products which are responsible for the introduction of cross links in the prepeptide and lan T responsible for the secretion of the peptide from the cell.

Mode of Action

Type A lantibiotics (e.g. nisin, epidermin) are flexible, elongated, amphipathic molecules which act mainly by forming pores in the bacterial cytoplasmic membrane. Type B lantibiotics (e.g. mersacidin, actagardine and cinnamycin), have a rigid globular shape and inhibit particular enzymes by forming a complex with their membrane-bound substrates. It can also inhibit the synthesis of peptidoglycan, the essential sugar – peptide backbone of the bacterial cell. When de novo synthesis of peptidoglycan is prevented, turnover processes lead to a drastic reduction of the cell wall thickness and eventually to cell lysis.

Advantages and Disadvantages

♦ Bacteriocins overcome some of the major issues with cationic host defense peptides including cost of goods since they are naturally produced by bacteria, and large scale fermentation/purification schemes have been developed.

♦ The unusual structures and amino acids of lantibiotics are very resistant to proteases.

♦ Lantibiotics have a proven safety history as peptides such as nisin have a long history in food preservation.

♦ Some lantibiotic peptides also have the ability to act as adjuvants.

♦ Disadvantage associated with the clinical use of nisin is its poor solubility at physiological pH. Despite this drawback, nisin in combination with lysostaphin has been shown to be an effective treatment for mastitis.

Application

Lantibiotics are attractive candidates for use in food industry (by inhibiting pathogens that cause spoilage) and the pharmaceutical industry (to prevent or fight infections in human or animals). The details of lantibiotics were given in the table -1

Conclusion

Although no lantibiotics are currently in clinical use, they represent an intriguing class of compounds with potential application in diverse range of therapeutic areas. The depth of diversity is likely to increase in coming years as more lantibiotics are discovered and advances are made in understanding the biosynthetic machinery. In vitro studies of individual enzymatic components are providing an insight into the enzymology at the molecular level, and could help in the development of more efficacious lantibiotic variants and further broadening of therapeutic targets through enzyme evolution. Meanwhile, perhaps one of the most promising features of this class of compounds is their favourable resistance profiles against Gram positive pathogens and, as such, current development is likely to focus heavily on the use lantibiotics as antibacterials.

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