学位論文抄録

Abstract of Thesis

Development of potent antipseudomonal β-lactams by means of polycarboxylation of aminopenicillins

（アミノペニシリンのポリカルボン酸化による抗緑膿菌性βラクタム剤の開発）

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Background and Purpose: Multidrug resistance has become a major concern worldwide. The β-lactam antibiotics are widely used to treat bacterial infections. However, if the offending pathogens are multidrug resistant (MDR), and their resistance to available antibiotics makes treatment difficult. Accumulating evidence has suggested that chemical modifications of antibiotic structures can alter drug metabolisms as well as therapeutic efficacies. In this context, a variety of β -lactam antibiotics have been developed via chemical modifications of naturally occurring β -lactams. Therefore, we have examined the effects of chemical modifications on amino groups of ampicillin-based β-lactams as well as amoxicillin in terms of antibacterial spectra which may pave the way to resolve the pathogenesis caused by Gram-negative MDR *P. aeruginosa.*

Objectives: The objective of this study was to establish and highlight the potential usefulness of the chemical modifications of β-lactam antibiotics and provide therapeutic alternatives to pave the way toward novel treatment options against MDR Gram-negative *P. aeruginosa* bacteria in the coming years.

Methods: I have synthesized a series of amino group modified aminopenicillins and determined the identities by means of chromatographic and mass spectrometric analyses. I have tested antibacterial activities of these derivatives against *P. aeruginosa* of laboratory strain PAO1 and of clinically isolated strains. I have tested the *in vivo* therapeutic efficacy of the modified amoxicillin in *P. aeruginosa* infection model.

Results: I have synthesized a series of amoxicillin derivatives by reacting amoxicillin with acid anhydrides in aqueous media. Purities and identities of the derivatives were confirmed by means of HPLC and mass spectrometry. All amoxicillin derivatives synthesized in this study showed stronger antipseudomonal activities compared to native amoxicillin both in the absence and the presence of tazobactam. Among the derivatives synthesized, diethylenetriaminepentaacetic acid (DTPA)-modified amoxicillin (DTPA-Amox) showed potent antipseudomonal activity not only against the laboratory strain PAO1 but also against clinically isolated *Pseudomonas* strains that were resistant to piperacillin and carbenicillin. DTPA-Amox had no obvious cytotoxic effects on cultured mammalian cells. In addition, in an *in vivo* model of leukopenia, DTPA-Amox treatment produced a moderate but statistically significant improvement in survival of mice with *P. aeruginosa* strain PAO1 infection.

Conclusion: Polycarboxylation by DTPA conjugation is an effective approach to enhance antipseudomonal activity of aminopenicillins. Thorough understanding of the mechanisms involved in polycarboxylation-induced enhancement of such antipseudomonal activity is necessary for the development of highly effective antipseudomonal agents.

Keywords: Antibiotics, drug resistance, Gram-negative bacteria, *Pseudomonas aeruginosa,* aminopenicillin, amoxicillin, semisynthetic antibiotics, leukopenia, penicillin binding protein, infection.