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Creation of antifungal antibiotics of new generation by chemical modification and genetic engineering methods – Modern approach to a solution of the problem of an antibiotic resistance at candidiasis infections

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Abstract

This review is dedicated to the research of modified antifungal antimycotics against candidiasis infectious. One of the key and urgent problems in modern medicine and pharmacology in recent decades has become the problem of ineffective action of antibiotics or the development of antibiotic resistance. Immunity of microorganisms to the action of antibiotics has led to the search for new effective drugs. Treatment of fungal infections, especially candidiasis, is also one of the most important problems in modern medical mycology. The solution of this problem is in the creation of new forms of antifungal drugs that will be more effective than their predecessors. Molecular transformation of antimycotics can be carried out by the help of chemical modification and genetic engineering. Chemically modified antifungals of new generation have already been tested. Among them pimaricin, amphotericin B, nystatin and lucenzomycin. The positive effect of these drugs on test-cultures of different types of candidiasis in vitro was shown.

Аннотация

Настоящий обзор посвящен исследованию модифицированных противогрибковых антимикотиков против инфекционного кандидоза. Одной из ключевых и актуальных проблем современной медицины и фармакологии в последние десятилетия стала проблема неэффективного действия антибиотиков или антибиотикорезистентности. Иммунитет организмов к действию антибиотиков привел к поиску новых эффективных препаратов. Лечение грибковых инфекций, особенно кандидоза, также является одной из важнейших проблем современной медицинской микологии. Решением этой проблемы стало создание новых форм противогрибковых препаратов, которые будут более эффективны, чем их предшественники. Молекулярная трансформация антимикотиков осуществлялась с помощью химической модификации и генной инженерии. Доступность молекул антибиотиков для химической модификации функциональными аминными и карбоксильными группами и создание производных с использованием генной инженерии позволяют получать новые лекарственные препараты с улучшенными физико-химическими свойствами для более целесообразного использования в клинике. Были испытаны химически модифицированные противогрибковые препараты нового поколения. Среди них пимарицин, амфотерицин В, нистатин и люцензомицин. Показано положительное влияние этих препаратов на тест-культуры различных видов кандидоза in vitro. Суммируя представленные данные, хотелось бы отметить, что создание новых химически модифицированных и генно-инженерных препаратов с более эффективными терапевтическими параметрами открывает новые перспективы для решения проблемы антибиотикорезистентности.

Keywords: Macrocyclic compounds, polyene antibiotics (PA), candidiasis, antibiotic resistance

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Irrational use of antibacterial antibiotics with a wide spectrum of action leads to fungal infections, where the main indicator is the development of resistance to pathogens of invasive mycoses[1,2]. Since the treatment of fungal diseases, especially invasive mycoses, is mainly associated with polyene antibiotics, which are the products of microorganisms from *Streptomyces genus* (Actinomycetes), the solution to this problem was in the formation of new forms of antifungal, that should be more effective drugs. This problem is acute in the treatment of fungal infections that were previously treated with polyene antibiotics (PA), such as amphotericin, nystatin, trichomycin and candidin. Due to changes in the environmental situation in nature, there are new forms of organisms possessing genetic mutations[3]. Accordingly, the compounds produced by them and their properties change in response to the selective pressure.

One of these changes is the resistance of organisms to these drugs, that is, they become antibiotic resistant. Thus, treatment of invasive fungal infections is becoming problematic. The most common of the mycoses is currently candidiasis caused by various representatives of the genus *Candida*. The solution of this problem is based on the search of new pharmaceuticals that can be obtained by the methods of genetic engineering and chemical modification of these molecules. Some chemically modified antibiotics of new generation such as pimaricin, amphotericin B, nystatin and others were investigated. Testing of benzyl derivatives of pimaricin on six cultures of the *Candida* showed that the greatest antifungal activity took place if the chemical radical in the molecule is a nitrogroup or halogen in the phenyl ring. These derivatives are more efficient against causative agent of candidiasis than initial pimaricin. The research of nanoderivatives of nystatin and pimaricin concerning a number of test cultures of the *Candida* was very efficiently conducted. These nanoderivatives have high antifungal activity in relation to fungi and considerably increase stability and biopharmaceutical properties of these antibiotics in relation to causative agents of candidiasis on the basis of the tested 11 species of the *Candida* – *C. albicans, C. utilis, C. tropicalis, C. crusei, C. glabrata, C.lusitaniae, C.lipolytica, C.norvegensis, C.parapsilosis, C. kefyr* and *C. guillermondii*[4]. Thus chemical modification of PA makes it possible to obtain less toxic derivatives of antibiotics with improved chemotherapeutic properties and with expanded spectrum of biological activity[5]. The search of pharmaceuticals with improved therapeutic properties led to the new modifications of most efficient antimycotic – amphotericin B. Initial amphotericin B has widest range of application and is one of most researched and used in practical medicine antifungal macrolide antibiotics. Various derivatives of amphotericin B and nystatin in liposomal form – lipid complexes and colloidal dispersed forms – have also been developed[6]. New liposomal amphotericin derivatives with low toxicity and high resistance have been developed[7], Amphotericin B kills pathogens of fungal infections by binding to the ergosterol of fungi. Modifying the structure of amphotericin B, it is possible to obtain its derivative, which would have the ability to bind only to ergosterol, but not to cholesterol. Modified version of amphotericin B can be synthesized from a natural product into three stages: with a total yield of up to 25%.

Modification of amphotericin B by benzoxaborols was carried out either by carboxyl group at the carboxyl group macrolactone ring at position C16 or at the amino group of the amino sugar (Figure 1). A series of hybrid compounds – mono- and dimodified derivatives of amphotericin B – are synthesized. The study of biological activity of these compounds revealed in most of them the high antifungal activity in vitro against *Candida* yeast cultures. The greatest activity was shown by the dimodified borol derivatives for which modification on a carboxyl group of C16 dimethylaminoethylamid was used (Figure 1). On some results, in particular, on activity, they surpassed initial amphotericin B[8]. Because of nephro- and gematoxicity attempts were done to modify its low-toxic derivatives on the basis of methods of chemical synthesis and genetic engineering[8,9]. New genetically engineered polyene macrolides were obtained as a result of genetically engineering experiments with the strain of microorganism *Streptomyces noursei*. The research of the molecular and genetic mechanism of action showed that under the influence of a liposomal form of amphotericin B there is a depression of biofilms formation by fungi of *Candida albicans* along with the block of a gene of MET3 expression. After daily incubation of biofilms with liposomal amphotericin B there was no MET3 gene mRNA transcribed that indicates the block of this one. Results of experiments show that the use of liposomal antimycotics is highly efficient concerning fungi of *Candida albicans* and give the chance to predict their application for increase in efficiency of pharmacological effect of antifungal medicines and decrease of their therapeutic dose. It should be noted that currently there are many low-toxic highly efficient semi-synthetic derivatives of PA. The greatest role belongs to nanotechnology, because nanotechnology research in medicine is based on the creation of a new generation of drugs that differ in a more effective way of their delivery to organs and tissues[10,11]. The selection of nanoderivatives of macrolide antibiotics with efficient antifungal activity was very important for the treatment of mycoses. The action of

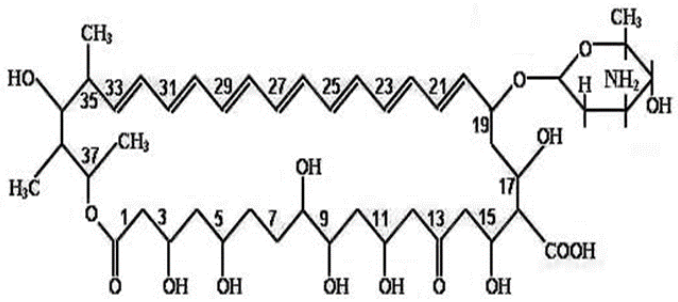

Figure 1 | The chemical structure of initial amphotericin B. Рис.1 Химическая структура исходного амфотерицина В.

nanoderivaives of tetraene PA nystatin and pimaricin was investigated on some test-cultures of yeast fungi *Candida*. It has shown that the above nanoderivatives have high antifungal activity to the pathogens of *Candida genus - C. albicans, C. tropicalis, C. crusei, C. glabrata, C. portugal, C. lipolytica, C. norvegensis, C. parapsilosis, C. akefyr and C. guillermondii*.

Thus, according to the results of different studies, it was shown that nanoderivatives of tetraene PA essentially rise stability and biopharmaceutical properties of these antifungal antibiotics[4,12].

Tetraene macrolide antifungal antibiotic lucenzomycin was first used by Italian researchers in the therapy of mycoses [13]. Lucenzomycin was obtained by microbiological synthesis from the organism Streptomyces lucensis. This antibiotic due to high toxicity has not been found an application in the drug therapy of mycoses, unlike nystatin and pimaricin. An obstacle in the systematic use of PA in medical practice is a relatively high toxicity (mainly nephrotoxicity), instability in storage, low solubility in water, as well as a decrease in sensitivity to pathogenic fungal microorganisms[14,15]. With this purpose we have synthesized low-toxic hydrophosphoryl sensimilla derivatives with high biological activity[15]. Studies on the search of new semisynthetic derivatives of lucenzomycin were continued and, as a result, relevant dialkylamidophosphate derivatives of this one have been obtained. Experiments on mice have shown that the acute toxicity of amidophosphate derivatives of lucenzomycin is 5 times less than that of the original antibiotic (LD50) and varies from 185 to 200mg/kg. Moreover, derivatives of lucenzolycin similar to nanoderivatives of pimaricin also have high antifungal activity against 11 test-cultures of yeast fungi of the Candida. It should be noted that amidophosphate derivatives contain in their molecules different chemical radicals $–CH_3$; C_2H_5; $CH_3(CH_2)_3$; C_6H_5; $\{Si(CH_3)_3\}_2$. It was shown that antifungal activity of first, forth and fifth compounds (i.e .with radicals CH_3, C_6H_5 and $\{Si(CH_3)_3\}_2$) exceeded activity of the original lucenzomycinin effects on *C. tropicalis, C. glabrata, C. parapsilosis* and *C. crusei*. Antifungal activity remained on the level of initial antibiotic against *C. albicans, C. utilis* and *C. guillermondii*. Activity of lucenzomycin derivatives is higher against these test-cultures[8,15-17]. However the action of amidophosphate derivatives of lucenzomycin on another *Candida* test-cultures (*C.lusitaniae, C.lipolytica, C.norvegensis, C. кefyr*) is less than that of original antibiotic [15-17]. For a long time, the causative agent of 90 % of *Candida* infections was considered *C. albicans*[16]. However in the recent years there has been an increase of Candida infections caused by *C. tropicali, C. parapsilosis, C. crusei, and C. glabrata*[1,17]. The high antifungal activity of some chemically modfied derivatives of lucenzomycin and their significantly low toxicity and better solubility in the water are important indicators that improve the biological, pharmacological and physical and chemical properties of these compounds in comparison with original antibiotic.

Concluding Remarks

A study of benzyl derivatives of pimaricin in six cultures of the genus *Candida* showed that these derivatives are more efficient against pathogens of candidiasis than initial pimaricin. Nanoderivatives of pimaricin and nystatin have high antifungal activity against these pathogens and significantly increase the stability and biopharmaceutical properties of these antibiotics in relation to the ones. The study of mono- and dimodified derivatives of amphotericin B show high antifungal activity in vitro against yeast cultures *Candida*. The use of liposomal antifungals is high efficient relative to the *Candida albicans* and make it possible to predict their use to improve the efficiency of the pharmacological action of these drugs and reduction of their therapeutic doses.

Thus the research of PA properties showed that biological activity is in the sharp dependence on chemical structure of molecules of these compounds[18,19]. The availability of antibiotic molecules to chemical modification by functional amine and carboxyl groups and the creation of derivatives using genetic engineering allow to obtain new pharmaceuticals with improved physical and chemical properties for more appropriate use in the clinic. Summing up the above data, we would like to note that the creation of new chemically modified and genetically engineered drugs with more effective therapeutic parameters opens up new prospects for solving the problem of antibiotic resistance.

Заключение

Исследование бензильных производных пимарицина в шести культурах рода Candida показало, что эти производные более эффективны против возбудителей кандидоза, чем исходный пимарицин. Нанопроизводные пимарицина и нистатина обладают высокой противогрибковой активностью по отношению к этим возбудителям и значительно повышают стабильность и биофармацевтические свойства этих антибиотиков по отношению к ним. Изучение моно-и димодифицированных производных амфотерицина В показало высокую противогрибковую активность in vitro в отношении дрожжевых культур Candida. Применение липосомальных противогрибковых препаратов является высокоэффективным по отношению к Candida albicans и позволяет прогнозировать их применение для повышения эффективности фармакологического действия этих препаратов и снижения их терапевтических доз. При этом исследование свойств ПА показало, что биологическая активность находится в резкой зависимости от химического строения молекул этих соединений.

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