Abstract

In recent years, fungal diseases have become a major medical problem. Invasive fungal infections due to their difficult diagnostics and treatment are a serious problem, which has been growing lately. Over a million people die every year because of complications of fungal diseases[1]. Increase in mycosis is caused by weakened immunity and increasing fungal drug resistance[2]. People with cancer, diabetes, AIDS or those taking immunosuppressive drugs are the most vulnerable to this infections[3].

Amphotericin B (AmB) is a polyene antibiotic used to treat endemic mycoses. AmB is used in the treatment of severe and chronic fungal diseases due to the broad spectrum of activity and rare pathogen resistance. It is called the "gold standard" in antifungal therapy[4]. For over 60 years, it has been used in treatment of fungal infections although it has severe side effects including nephrotoxicity, hepatotoxicity or even death[5]. The molecular mechanisms of action of antibiotic has not been fully understood, that is why AmB is being examined in many laboratories around the world. Understanding the molecular processes responsible for the activity of the molecule would minimize the side effects of antibiotic while maintaining its high efficiency.

The dissertation involved studies aimed at understanding the molecular mechanisms of toxicity of AmB. It has been stated that therapeutic and toxic effects of antibiotic depend on the molecular organization of AmB molecules. Techniques used to determine the organization and orientation of the antibiotic included: absorption and emission spectroscopy as well as fluorescence lifetime imaging microscopy and Raman scattering microscopy. Studies were carried out on model lipid membranes, fungal cells and animal cell lines.

Results of experiments confirmed by molecular dynamic studies indicate that the composition of the lipid membrane affects the molecular organization of AmB. In addition, the presence of sterols determines the incorporation of an antibiotic into the lipid membrane in the form of aggregates that could create ion channels. Mechanisms of defense of fungal and human cells against the antibiotic have been observed and based on removal of AmB by structures called "sponges" or exosomes. The results of studies indicate that reducing the toxicity of an antibiotic should prevents its aggregation. It has been deduced that reduction of the toxicity of an antibiotic should base on regulation of expression of proteins responsible for sterol distribution in human cells, combining antibiotic with transporting proteins and nanoparticles.

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