Elucidating the ion channel structure of the antibiotic amphotericin B, solving a 50-year-old mystery

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Abstract

Fungal infections are highly lethal, as in the case of mucormycosis (see below). The mechanism of action of selective toxicity of drugs against fungi is quite different from that of bacteria, making the development of therapeutic agents difficult. Amphotericin B (AmB, Fig. 1) is an antibiotic that can be used to treat serious systemic infections, and the ion channels formed by AmB, together with ergosterol (Erg, Fig. 1) in the fungal cell membrane, are responsible for its fungicidal action. Since the 1970s, the detailed structure of this ion channel has remained unknown. The authors turned to solid-state nuclear magnetic resonance (Fig. 2) to solve this conundrum, and succeeded in measuring the number of molecules and the distances between the isotope-labeled sites of AmB. Based on this information, and with the help of molecular dynamics simulations, the authors were able to elucidate the entire ion channel structure (Fig. 2).

Background & Results

The ion channel structure elucidated in this study allows us to rationally explain the pharmacological effects and serious side effects of AmB. In other words, it may serve as key information for the development of AmB derivatives with reduced side effects and new antifungal drugs. The approach used in this study also provides important clues to the remaining difficult questions concerning the mechanism of action of pharmacologically active substances.

Significance of the research and Future perspective

AmB has long been used as a reliable therapeutic agent because of its excellent antifungal activity against a wide spectrum of pathogenic fungi and yeasts. For example, persons infected with novel coronaviruses with compromised immune functions often become infected with environmental fungi. In particular, a fungal infection called mucormycosis is highly lethal and has become a major problem in India. AmB is widely used for its treatment and has saved many lives. On the other hand, AmB has serious side effects such as nephrotoxicity, which has been a major clinical problem. The mechanism of pharmacological action and side effects of AmB must be elucidated to overcome the adverse effects.

The results of this research have clarified the structure of ion channels, the main entity responsible for the pharmacological effect of AmB. It is expected that the development of AmB derivatives with reduced side effects will be possible in the future based on the channel structure. It has first been disclosed that the lifetime of molecular aggregates required for further assembly of the channel aggregates and stable expression of pharmacological activity differs between the two sterol membranes is a key point to improve the selective toxicity of AmB (Fig. 3). The combination of experiments and calculations used in this study and the ideas for the mechanism of activity expression are expected to provide insight into the remaining difficult questions regarding the mechanism of drug action.

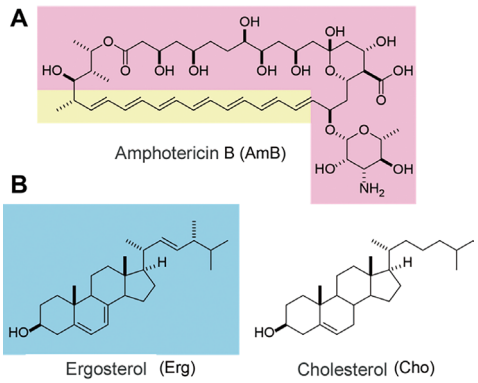

Figure 1. Chemical structure of AmB and Erg. AmB molecules form ion channels only in fungal biomembranes containing Erg. On the other hand, AmB also interacts with Cho in human cell membranes, causing side effects.

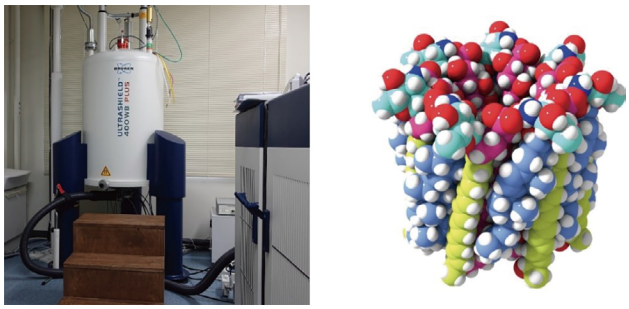

Figure 2. 3D molecular configuration information was obtained using a solid-state NMR system (left), and the structure was assembled to satisfy these requirements (right).

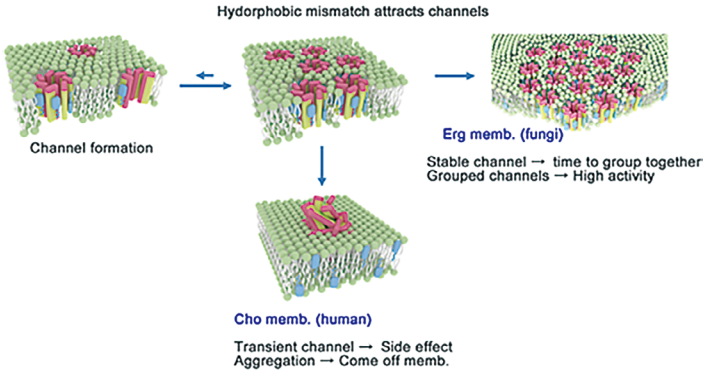

Figure 3: Hypothesized mechanism by which ergosterol and cholesterol produce different pharmacological effects and side effects of AmB, respectively. In fungal Erg-containing cell membranes, the ion-permeable AmB-Erg aggregates are sufficiently stable and can migrate through the membrane to form large aggregates (the body of pharmacological action, far right). On the other hand, in human Cho-containing cell membranes, the stability of AmB-Cho aggregates is insufficient, and AmB aggregates irregularly before forming large aggregates, which do not show effective ion permeability.

Patent

Treatise Umegawa, Yuichi; Yamamoto, Tomoya; Dixit, Mayank et al. Amphotericin B assembles into seven-molecule ion channels: An NMR and molecular dynamics study. Science Advances 2022, 8(24), eabo2658. doi: 10.1126/sciadv.abo2658
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