

Molecular modelling of membrane activity of Amphotericin B, the polyene macrolide antifungal antibiotic

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Amphotericin B (AmB) is a well known polyene macrolide antibiotic used to treat systemic fungal infections. Despite its toxicity (mainly nephrotoxicity) AmB is still regarded as a life saving drug in deep seated fungal infections because there are no better alternatives. Apart from its toxicity, AmB exhibits several positive features indispensable for the effective antifungal drug i.e.: i) high antifungal activity, ii) broad antifungal spectrum, iii) fungicidal activity, and iv) very rare induction of fungal resistance as well as the ability to overcome multidrug resistance of fungi. None of other antifungal drugs exhibit these positive chemotherapeutic features together. Therefore, AmB still may be regarded as a promising candidate or rather lead compound for the development of less toxic drugs, which will be new generation of derivatives of parent molecule. However, the lack of adequate knowledge of the AmB mechanism of action is a serious obstacle to efficiently develop of new derivatives. Several decades of studies on this mechanism revealed that biological action of AmB is very complex. Cell membrane is a site of action for this antibiotic. AmB interacts with membrane components and forms trans-membrane channels that disturb barrier function of the membrane. The channels are responsible for induced cation leakage that eventually leads to cell death. According to the most popular sterol hypothesis, sterol molecules are indispensable for AmB action in the membrane. It is also regarded that chemotherapeutic application of the antibiotic is based on higher affinity/activity of AmB towards membranes containing ergosterol (in fungal membranes) than cholesterol (in human membranes). Unfortunately, detailed molecular mechanism of action of AmB in the membrane is not known. Therefore, complementary to different experimental approaches, computational chemistry methods were used to study AmB mechanism of action. These molecular modelling/computational chemistry efforts were undertaken in several laboratories but the contribution of our group to the field brings new essential data. Lasting a decade programme that was run at our Department covered studies of: i) molecular properties of AmB and its membrane targets, ii) membrane AmB channels, and iii) different modes of interaction of AmB with the membrane. Currently the studies include also AmB derivatives which exhibit lower toxicity than parent molecule. In particular, molecular dynamics studies of AmB membrane channels revealed that free carboxyl and amino groups form the chain of intermolecular hydrogen bonds within the channel. These two groups are main targets for chemical AmB modifications and consequently their interactions within the channel may be influenced in order to get more selective drug. It was also found that structure of channels build from AmB and ergosterol is substantially different than channels build from AmB and cholesterol molecules. Analysis of interaction between AmB and the membrane surface shows specific orientation of AmB at the surface. The latter results indicate that single AmB molecule is not prone to enter the membrane. This may support hypothesis that supramolecular structures that are formed on the membrane surface may be responsible for action of AmB inside the membrane. Altogether, performed studies revealed many details concerning molecular properties of the antibiotic and its derivatives as well as their interactions with the membrane. Obtained results may help to understand the AmB mechanism of action on molecular level and eventually to design new less toxic AmB derivatives.