Interaction of the macrolide antibiotic azithromycin with model of membranes

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ABSTRACT:
Purpose and methods: The aim of the study was to investigate the influence of azithromycin on the lateral organization of lipids, their phase transition, and the bending modulus of bilayers using real-time atomic force microscopy (AFM) on dioleoylphosphatidylcholine: didodecyldimethylphosphatidylcholine (DOPC:DPPC) bilayers, differential scanning calorimetry (DSC) on multilamellar vesicles, (MLV) and micropipet experiments on DOPC giant unilamellar vesicles.

Results: 1) Phase separation was observed between gel domains of DPPC and fluid matrix of DOPC. Time-lapse images collected following addition of azithromycin revealed progressive erosion and disappearance of DPPC gel domains within 60 minutes. 2) Calorimetric experiments on DPPC and DOPC vesicles showed a suppression of the pretransition and a phase separation respectively. 3) The micropipet experiments on DOPC giant vesicles revealed a bending modulus divided 2 times. At higher molar ratio of antibiotic (lipid:antibiotic ratio = 50:1), we observed a strong modification in the shape of the vesicles and their potential destruction.

Conclusion: This study could help us to elucidate the physico-chemical membrane properties underlying the effect of drugs on biological processes like inhibition of endocytosis and lysosomal phospholipase activity.

INTRODUCTION:
Azithromycin is a dicationic macrolide antibiotic derived from erythromycin A, with a marked amphiphilic character. It was shown to decrease the lysosomal phospholipase activity and to inhibit endocytosis1. These effects are related to the ability of azithromycin to interact with lipids and alter the biophysical properties of membranes2. In this study, we further investigated the effect of azithromycin on DPPC, DOPC, and DOPC:DPPC bilayers.

AFM on DOPC:DPPC 1:1 bilayers :

DPPC gel domains (white) in DOPC fluid matrix (dark) : eight difference:1.10±0.05 nm

Addition of azithromycin + 60 mn : only one uniform fluid phase visible

DSC on DOPC and DPPC MLVs :

Suppression of the DPPC pretransition
Phase separation of vesicles enriched with azithromycin or not
Strong decrease of the enthalpy change gel-fluid phase for both DOPC and DPPC

Micropipet experiments :

Action of azithromycin on bilayers :
• interaction of azithromycin with polar head groups
• fluidification of DPPC at the DOPC-DPPC interface
• decrease of the enthalpy associated to the gel-fluid phase transition
• enhancement of the fluctuations of the bilayers by mecanical effect of the insertion of azithromycin molecules between the polar head of DOPC molecules

References :