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On the interaction between fluoxetine and lipid membranes: effect of the lipid composition

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Abstract

Molecular interaction between the antidepressant fluoxetine and lipid bilayers was investigated in order to provide insights into the drug's incorporation to lipid membranes. In particular, the effects of lipid's unsaturation degree and cholesterol content on the partitioning of fluoxetine into large unilamellar vesicles (LUVs) comprised of unsaturated 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC) and saturated 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC) were evaluated using second derivative spectrophotometry and Attenuated total reflection-Fourier transform infrared spectroscopy (ATR-FTIR). It was found that fluoxetine partitioned to a greater extent into the liquid-crystalline DOPC LUVs than into the solid-gel DPPC LUVs. The lipid physical state dependence of drug partitioning was verified by increasing the temperature in which the partition coefficient of fluoxetine significantly increased upon the change of the lipid phase from solid-gel to liquid-crystalline. The incorporation of 28 mol% cholesterol into the LUVs exerted a significant influence on the drug partitioning into both DOPC and DPPC LUVs. The ATR-FTIR study revealed that fluoxetine perturbed the conformation of DOPC more strongly than that of DPPC due to the *cis*-double bonds in the lipid acyl chains. Fluoxetine possibly bound to the carbonyl moiety of the lipids through the hydrogen bonding formation while displaced some water molecules surrounding the PO_2^- regions of the lipid head groups. Cholesterol, however, could lessen the interaction between fluoxetine and the carbonyl groups of both DOPC and DPPC LUVs. These findings provided a better understanding of the role of lipid structure and cholesterol on the interaction between fluoxetine and lipid membranes, shedding more light into the drug's therapeutic action.

Keywords: *Fluoxetine, Second derivative spectrophotometry, ATR-FTIR, Unsaturation degree, Cholesterol.*