Effect of phospholipid headgroup on the “flip-flop” of Cholesterol

Drew Marquardt,[1] Norbert Kučerka,[2] Thad Harroun,[1] and John Katsaras[2,3]

[1] Department of Physics, Brock University, St. Catharines, ON, Canada
[2] NRC Canadian Neutron Beam Centre, Chalk River Laboratories, Chalk River, ON, Canada
[3] Neutron Sciences Directorate, Oak Ridge National Laboratory, Oak Ridge, Tennessee , USA

Cellular membranes are the barrier which separate the inside of a cell with its environment. The main structural component of the cell membrane is lipids. How lipids interact with membrane bound molecules and other lipids is of great interest to the field of bio-sciences. Past neutron diffraction experiments performed at the CNBC have demonstrated that cholesterol re-orientates itself from an upright position to lying parallel to the plane of the bilayer in polyunsaturated fatty acid containing phospholipids (PUFA).[1] Upon the addition of ordered phospholipid dopant, such as 14:0/14:0 PC or 16:0/18:1 PC, cholesterol re-orients itself to the upright position.[2] In these studied di-20:4 PC was the PUFA utilized, which required 5 mol% of 14:0/14:0 PC or 50 mol% 16:0/18:1 PC to cause the cholesterol “flip-flop”.[2]

It has been theorized that large headgroups allow for more cholesterol to be accommodated by the phospholipid than smaller headgroups. Authors have referred to this theory as the “Umbrella” model. According to this hypothesis it will take more dopant phospholipids to re-orient cholesterol if it has a smaller headgroup than phosphotidylcholine (PC). In this study the small neutrally charged headgroup phosphotidylethanolamine (PE) was used. For direct comparison with previously published results di-20:4 PC was the PUFA.

The neutron data illustrates a higher concentration of 16:0/18:1 PE was NOT needed for the re-orientation of cholesterol when compared to the amount 16:0/18:1 PC required. The PE re-orientation was observed to occur between 50 mol% and 60 mol% 16:0/18:1 PE, which is approximately the same amount dopant needed to flip cholesterol in 16:0/18:1 PC environments. The observed re-orientation of cholesterol with small headgroups does not support the umbrella model as hypothesized. This result suggests that cholesterol’s unique behavior is due solely to the composition of the phospholipid acyl chains.

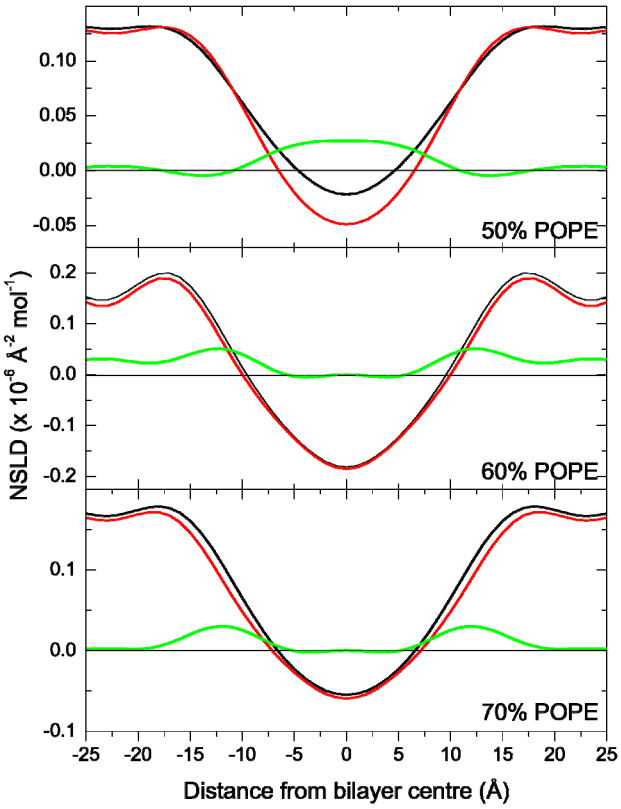

Fig. 1 Neutron scattering length density distribution of bilayers composed of DAPC+10% cholesterol doped with 50 mol% POPE (top panel), 60 mol% POPE (middle), and 70 mol% POPE (bottom panel), all hydrated with 8% D_2O. Samples containing deuterium-labelled cholesterol are shown in black, while un-labelled cholesterol is shown red. The green lines represent the cholesterol deuterium-label mass distribution (black-red) for each respective sample.

References

[1] T.A. Harroun, J. Katsaras and S.R. Wassall. *Biochemistry* **45,** 1227 (2006).

[2] N. Kučerka, D. Marquardt, T.A. Harroun, M.-P. Nieh, S.R. Wassall, D.H. de Jong, L.V. Schafer, S.J. Marrink and J. Katsaras, *Biochemistry* **49**, 7485 (2010).