Experimental report

15/02/2021

Proposal: 9-13-894 **Council:** 10/2019

Title: Can impaired lipid exchange be in part responsible for the atherogenic properties of ApoE4?

Research area: Soft condensed matter

This proposal is a resubmission of 9-13-807

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Samples: Cholesterol
Deuterated DMPC
ApoE3 reconstituted HDL

Instrument	Requested days	Allocated days	From	To
D17	1	0		
FIGARO	1	1	24/02/2020	25/02/2020

Abstract:

Atherosclerosis, and its clinical consequences of heart attacks and strokes, is the largest killer in the west. Levels of high and low-density lipoproteins (HDL and LDL, respectively) in the blood have been shown to be directly related to the development of this disease. These particles remove or deposit lipids from artery walls, however much about this process is unknown. Therefore, determining and understanding the importance of the bilayer composition and lipid phase is fundamental in the treatment of the disease. The aim of this study is to gain insight into effect the bilayer composition has on the exchange rate of lipids with the HDL mimics, and compare the role of the apolipoprotein present to help determine the specific roles of each of the components in turn.

Experimental Report for experiment: **9-13-894**

Can impaired lipid exchange be in part responsible for the atherogenic properties of ApoE4?

The aim of the experiment was to determine if ApoE3 and ApoE4 have different lipid exchange abilities when incubated with model membranes. We investigated the effect of saturation in the bilayer and the presence of cholesterol, we also looked at ApoE protein alone or as reconstituted HDL particles.

During our beam time we measured samples of ApoE3 and ApoE4 proteins alone interacting with DMPC, both in the presence and absence of cholesterol, and POPC bilayers, which provided us with information on their behaviour with differing lipid types. Whilst similarities were observed for the interaction of both ApoE3 and ApoE4 protein with DMPC, differences were seen when interacting with POPC, see figure 1. We had previously measured ApoA1 protein interacting with DMPC which showed something different again from both ApoE proteins, however we require measurements of ApoA1 protein interacting with DMPC+cholesterol and POPC to complete this data set.

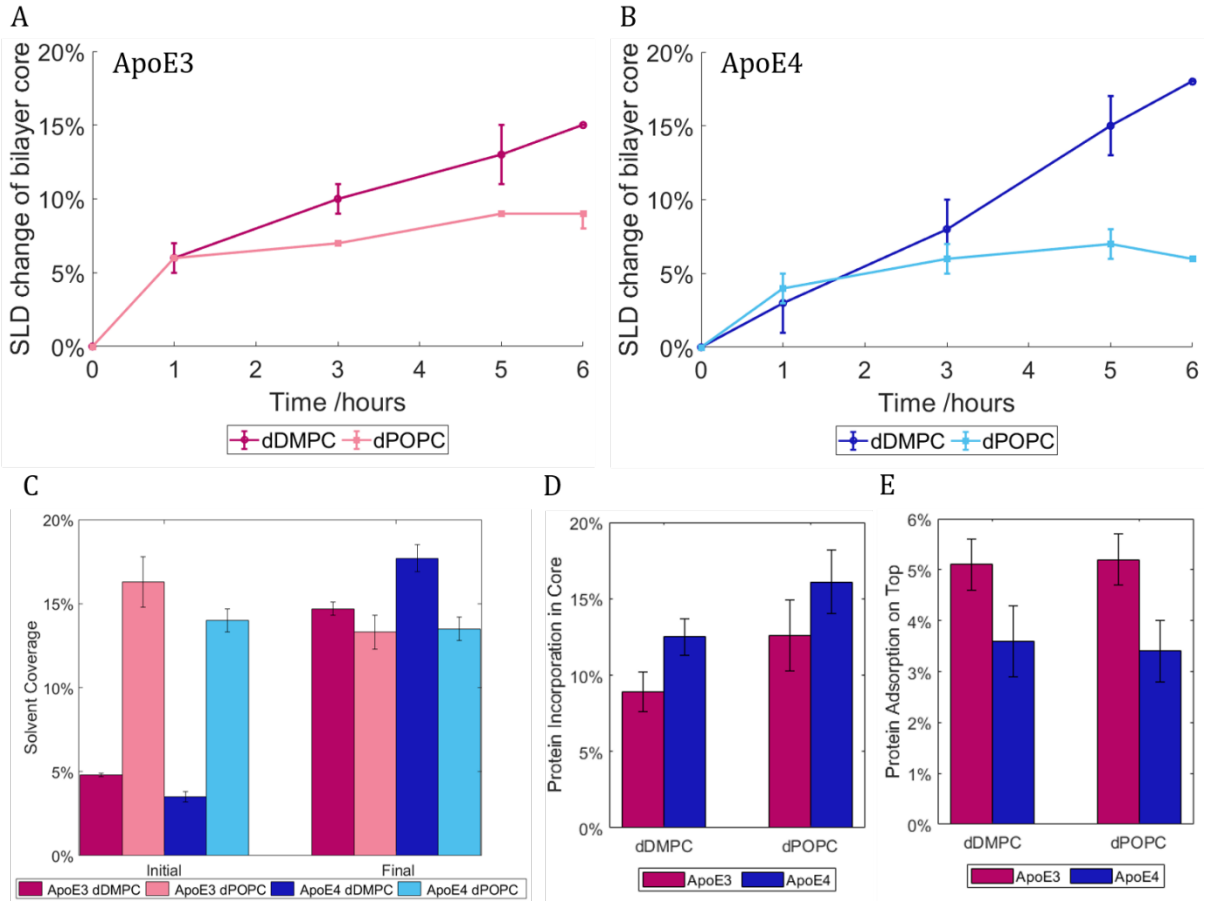

Figure 1. Summaries of NR data for the incubation of ApoE3 (A) and ApoE4 (B) with DMPC and POPC bilayers, kinetic data of lipid replacement in terms of change in SLD of the lipid core. Relative changes in solvent coverage of the bilayers (C), protein incorporation in the core (D) and protein adsorption on top of the bilayers (E) are also given.

We also measured ApoE3-, ApoE4- and ApoA1- based reconstituted HDL particles against various bilayers in the presence and absence of cholesterol. Differences were clearly seen when comparing the particles made with each of the proteins. From the analysis it can be seen that in terms of lipid removal, no clear pattern was observed for ApoE3- and ApoE4-rHDL, however ApoA1-rHDL behaved in a more similar way to HDL. In terms of lipid exchange ApoE3- and ApoE4-rHDL removed significant portions of the bilayers, as did ApoA1-rHDL again behaving in a similar way to native HDL. The presence of cholesterol in the bilayers hindered the rHDL ability to exchange lipids as seen previously with native HDL and LDL. The use of both deuterated and non-deuterated cholesterol in the bilayers allowed for the distinction between if cholesterol was specifically targeted in the exchange. No difference was seen between these bilayers, implying the cholesterol was not targeted and the exchange was of phospholipids only, see figure 2.

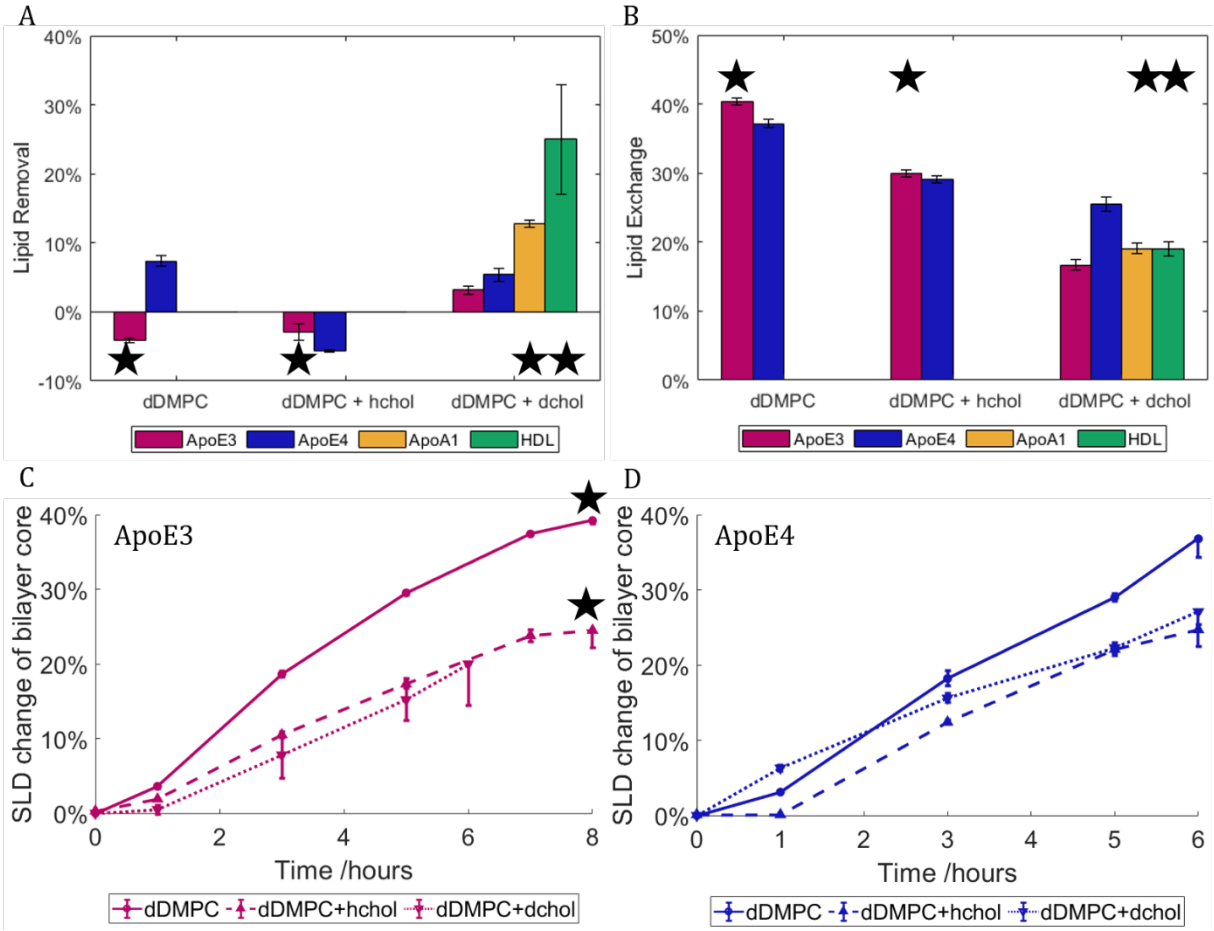

Figure 2. Summaries of NR data for the incubation of ApoE3-, ApoE4-, ApoA1-rHDL and HDL against model membranes, showing quantities lipid removal (A) and lipid exchange (B). Kinetic data of lipid exchange for ApoE3- (C) and ApoE4-rHDL (D highlighting the reduction in exchange seen in the presence of cholesterol and highlighting no difference seen between deuterated and non-deuterated cholesterol.

The data here has been submitted for publication.