Experimental report

17/02/2020

Proposal: 9-13-807 **Council:** 10/2018

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

Research area: Biology

This proposal is a new proposal

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Samples: deuterated phospholipids
Protein (ApoE3/E4)

Instrument	Requested days	Allocated days	From	To
D17	4	0		
FIGARO	4	5	14/06/2019	17/06/2019
			13/09/2019	14/09/2019
			16/09/2019	17/09/2019

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: **9-13-807**

Atherosclerosis is the leading cause of death in western society, its consequences of cardiovascular diseases (CVDs) such as strokes and heart attacks arise from the build-up of plaque which accumulates in the artery walls. Lipoprotein particles have been shown to play a role in this development, however mechanistic details of this process are missing. Specific apolipoprotein variants present in lipoprotein particles have been shown to either provide a protective or a detrimental effect in this development process, therefore understanding the influence of lipoprotein composition and in particular the apolipoprotein variant present is of utmost importance in understanding the initial development processes in CVDs, which in turn has knock on effects in the diagnosis and treatment possibilities of the disease, especially as clinical lipid profiling today fails to predict the risk of development to this disease. In this project, by determining the specific effects the reconstituted HDL and bilayers compositions have, with initial studies focussing on apolipoprotein variants ApoE3 and ApoE4, a deeper understanding of the initial plaque build-up at the onset of atherosclerosis will be enabled.

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. The presence of cholesterol in the bilayer also altered this interaction. 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.

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. On initial analysis it can be seen that the most exchange which occurred was on interaction with ApoA1-based particles (Figure 1), however differences were also seen between ApoE3 and ApoE4 interactions between bilayers. The presence of cholesterol also affected the rate of exchange – a reduction in the overall quantity of lipids exchanged was observed.

Whilst clear impacts from the varying compositions can be seen, no clear trends are attainable thus far as we are still missing vital datasets. Some beamtime has been awarded due to losing time at the beginning of the previous cycle (which we are due to carry out this cycle, Feb 2020) to continue this story looking into the effect of the different protein types, however we are looking to obtain a further beamtime to complete the datasets of differing bilayers compositions and HDL particles to publish later this year.

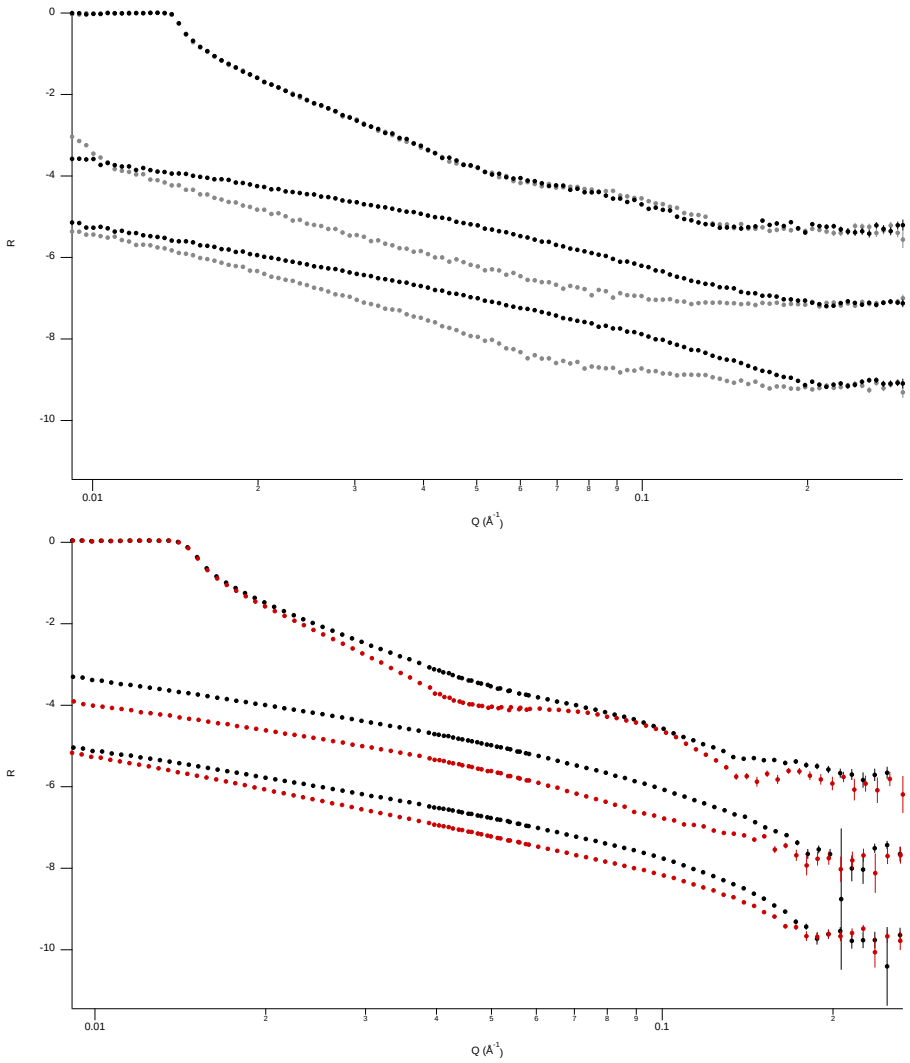

Figure 1. NR data for the incubation of POPC (above, grey symbols)- and DMPC (below, red symbols)-based ApoA1 HDL particles against dDMPC and dDMPC+20%moCholesterol SLB in H_2O, respectively (black symbols correspond to pristine SLB). Data collected at Inter in May 2018 and Figaro in Sep 2019.