COMPARISON OF NEUTRAL AND CHARGED HIGH DENSITY LIPOPROTEIN USING BIMODAL NANOPARTICLES

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Introduction

Early diagnosis of plaque formation will increase the efficacy of interventional therapies, thereby improving survival rates. To this aim several molecular imaging techniques have been developed in recent years. In this study contrast agents based on high density lipoprotein (HDL) were used. The protein component of HDL apolipoprotein A-I (Apo A-I) is known to target specific receptors on activated macrophages. Therefore, previous studies have demonstrated the ability to visualize macrophage rich regions using HDL agents. Since macrophage burden in atherosclerosis is an indicator for inflammation severity and believed to significantly contribute to plaque instability, these HDL agents may contribute to achieve the abovementioned aim of early detection.

Natural HDL has a close to net zero charge (around -10mV) and the aim of this study was to synthesize and compare two different HDL-based contrast agents, one with the negatively charged Gd-DTPA-DMPE and one with the neutral Gd-DOTA-C14 incorporated, and thus investigate the effect of charge.

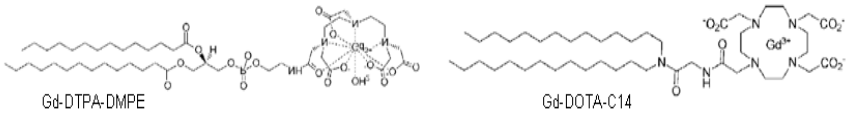
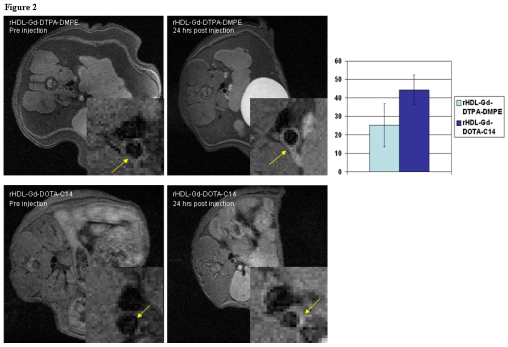


Figure 1

Methods

The HDL-like nanoparticles were synthesized as described previously and fully characterized in terms of size, relaxivity, cholesterol efflux capacities and uptake by macrophages. *In vivo* pharmacokinetics studies were performed on atherosclerotic apoE-KO mice, while HDL uptake and MRI signal enhancement of the lesioned vessel wall of these animals were compared between both agents. The abdominal aorta of the animals was scanned in a 9.4T animal scanner, prior and 24 hours post intravenous administration of the different agents, using a T_1-weighted fat-saturation sequence. After *in vivo* imaging, the mice were sacrificed and full quantitative optical analyses of the different tissues were done.

Figure 2



Results

The sizes of both particles were determined to be within the range of natural HDL and they were not significantly different from each other. The zeta potential, a measure for the surface charge of the particles, was determined and revealed that rHDL-Gd-DOTA-C14 is less negatively charged than rHDL-Gd-DTPA-DMPE. The zeta potential values were found to be -39.6 mV and -9.5 mV for rHDL-Gd-DTPA-DMPE and rHDL-Gd-DOTA-C14, respectively, which for rHDL Gd-DOTA-C14 is comparable to surface charge of native HDL. *In vivo* MRI showed that the neutral DOTA based HDL particle gave rise to a significantly higher percentage of the vessel wall area with enhancement (fig. 2). This was validated by *ex vivo* NIR imaging experiments that revealed the DOTA based agent to be taken up more avidly throughout the aortas (Fig. 3). The organs of two mice for each agent were analyzed using near infrared (NIR) fluorescence imaging for which the acquired images are shown in figure 4A. Relative average fluorescent values for each organ are displayed in figure 4B. Fluorescence in the liver was found to be highest and comparable for both agents, while the DOTA-based HDL interestingly showed a lesser accumulation in the lungs.

Figure 3

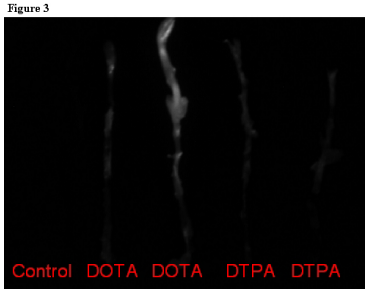
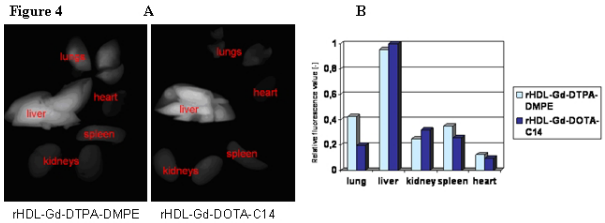


Figure 4



Conclusion

We here present a comparison between charged and neutral HDL contrast agents, in which we observed that the neutral agent based on Gd-DOTA yielded greater MR contrast in the mouse aortas. Furthermore we observed greater accumulation of the charged Gd-DTPA based agent in the lungs. As natural HDL is also almost neutral, it is likely that rHDL-Gd-DOTA-C14 better reflects the behavior of natural HDL than rHDL-Gd-DTPA-DMPE.