The measurement of the characteristics of the metabolic syndrome and the effect of a targeted treatment of rosiglitazone

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Introduction:

The metabolic syndrome is a chronic metabolic problem that is characterized by disturbed blood glucose levels, high blood pressure and elevated triglyceride levels. Rosiglitazone used to be a commonly prescribed drug for diabetes, with potential additional benefits by reducing atherosclerosis. However, rosiglitazone is now restricted in the U.S. (1) and suspended in Europe (2), because of serious cardiovascular side effects. The main sites of action for rosiglitazone are the liver and atherosclerotic plaques, sites that are known to passively accumulate liposomal formulations (3). Therefore, we wanted to investigate whether liposome encapsulation of rosiglitazone would improve the cardiovascular side effects, while preserving the therapeutic response.

The objectives of this study were: 1. to establish whether rosiglitazone administration causes cardiac dysfunction in a mouse model. 2. to establish whether liposome-encapsulation reduces these side effects, if present, and 3. to investigate whether liposomal delivery of rosiglitazone preserves the therapeutic response compared to standard rosiglitazone.

Methods:

Micelles incorporating rosiglitazone and Gd-DTPA-BSA were prepared using lipid film hydration.

In vivo: therapeutic effects were tested in LDLr-/- mice.

The mice were randomized to 4 treatment groups based on plasma lipids, Mice were exposed to either a chow or a high fat diet for 26 weeks, with treatment starting at week 16 and lasting the remaining 10 weeks:

Group 1 (n=8). Healthy control (chow diet)
Group 2 (n=30) High fat control (HFD) (n=15 sacrificed as initial control at 16 weeks)
Group 3 (n=15) Oral rosiglitazone (HFD + rosiglitazone) (10 mg/kg bw/day)
Group 4 (n=15) Rosiglitazone micelle with osmotic pumps (10mg/kg bw/day) on HFD

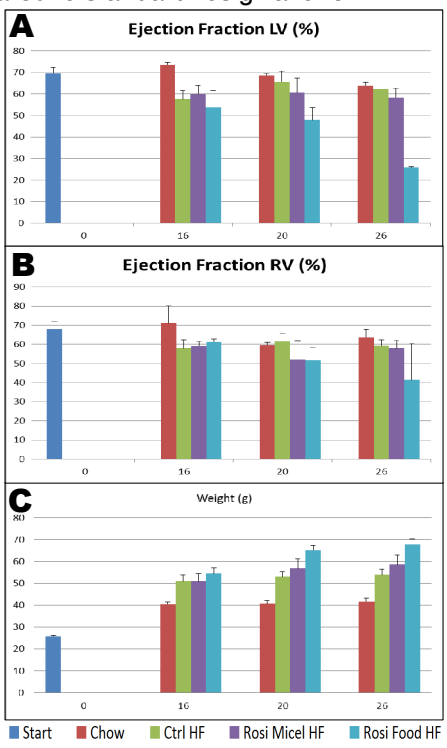
Animals were weighted and blood was sampled every 4 weeks, and MRI measurements were performed on t= 0, 16, 21 and 26 weeks.

MRI: Self-gated cine FLASH (9 slices, 18 frames) was used for the heart function measurements, a T2-weighted fast spin echo scan was used for used for the abdominal fat measurement and a T1-weighted retrospectively-gated FLASH sequence (Intragate) to assess micelle targeting and determine the therapeutic effect on atherosclerotic plaques. Liver metabolites were assessed using a PRESS sequence. All experiments were performed on a 7T Bruker PharmaScan.

Post-mortem Mice were perfusion-fixated and heart, aorta, and liver were collected for histological analysis.

Analysis Heart function was determined by drawing all left and right endocard and epicard borders using Mass4Mice. Blood samples were tested for cholesterol and triglyceride levels. Data are represented as the mean ± SEM.

Statistical analyses were done with a t-test (paired, 2 samples unequal variance).



Results & discussion:

The heart function analysis showed a progressive cardiac dysfunction in the rosiglitazone-treated mice compared with the chow-fed and HFD-fed mice, apparent from an increased end systolic volume (ES) of the left and right ventricle, an increased end diastolic volume (ED) of left and right ventricle, an increased ventricle volume and decreased left and right ejection fractions ($P<0.05$), indicating a dilated cardiomyopathy (Fig A, B). In contrast, the rosiglitazone micelle-treated group showed no significant differences in heart function compared to the HFD group, indicating that micelle-encapsulation of rosiglitazone indeed mitigates the adverse side effects of this drug.

A second known side effect of rosiglitazone is significant weight gain. Indeed, rosiglitazone-fed mice gained about 24% body weight over the 10 week treatment, significantly more than the rosiglitazone-micelle and HFD-fed groups did (they gained 15% and 6% respectively) (Fig C). The weight gain did not result in changes in blood cholesterol and triglyceride levels. We are currently analyzing the remaining data to establish whether micelle-encapsulated rosiglitazone has a therapeutic effect on liver fat, metabolic profile, and atherosclerotic plaque development.

Conclusions:

This study shows that MRI is a tool that can be used to assess the diverse aspects of metabolic syndrome. We showed that rosiglitazone at a standard clinical dose induces dilated cardiomyopathy and weight gain in the LDLr-/- mouse model. Micelle encapsulation of rosiglitazone significantly improves these unwanted side effects.

References

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