Glycosphingolipids and atherosclerosis
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Summary

The studies presented in this thesis report on the effects of pharmacological modulation of glycosphingolipids on different manifestations of the metabolic syndrome.

In chapter I we provide the background information for this thesis. The Metabolic syndrome is a constellation of metabolic deviations manifesting clinically as atherosclerosis, diabetes and non-alcoholic fatty liver disease. Atherosclerosis is the major cause for coronary artery disease and it represents a complex pathology involving dysfunction in lipid metabolism and chronic inflammation. High cholesterol concentration in plasma is an important risk factor for atherosclerosis and the main current therapies target cholesterol synthesis and homeostasis. Glycosphingolipids (GSL) are a wide class of lipids mainly found in cellular membranes. Several experimental evidences, points to a link between atherosclerosis and glycosphingolipid abnormalities. The iminosugar AMP-DNM is a potent inhibitor of glucosylceramide synthase (GCS), key enzyme in glycosphingolipid biosynthesis. AMP-DNM treatment of rodent models for the metabolic syndrome resulted in ameliorated diabetes and liver steatosis and improved cholesterol homeostasis. These beneficial effects of AMP-DNM and the existing literature on GSL and atherosclerosis give us the rationale for the studies further presented.

Chapter II describes a study on the effect of AMP-DNM treatment on prevention of atherosclerosis. APOE3*Leiden and LDLR (-/-) mice were fed with a diet rich in cholesterol containing or not AMP-DNM. The iminosugar prevented hyperlipidemia, generated a less atherogenic lipid profile, and induced a dramatic reduction in the development of atherosclerotic lesions. The effect of AMP-DNM was associated with improved cholesterol homeostasis, an increase in bile secretion and enhanced excretion of cholesterol in the feces and a decrease in inflammatory markers. All these factors contributed to the observed inhibition in plaque formation.

AMP-DNM is not inhibiting specifically GCS, but also the lysosomal and non-lysosomal glucocerebrosidases, GBA1 and GBA2. The idose-analogue of AMP-DNM, L-ido-AMP-DNM, similarly inhibits GCS and GBA2; however, it hardly inhibits GBA1 in contrast to AMP-DNM. In chapter III we compared the efficacy of AMP-DNM and L-ido-AMP-DNM in preventing the development of atherosclerosis in LDLR (-/-) mice receiving an atherogenic diet for 12 weeks. We observed that only AMP-DNM prevented markedly lesion development. In contrast to AMP-DNM, L-ido-AMP-DNM hardly caused increased biliary and fecal cholesterol excretion. Our results suggest that the potent anti-atherogenic effect of AMP-DNM requires concomitant inhibition of GBA1.

Given all the beneficial actions of AMP-DNM observed in the studies on preven-
tion of atherosclerosis, we investigated if this iminosugar would be also able to halt the progression and/or induce regression of existing atherosclerotic lesions (chapter IV). In this study, we treated LDLR(-/-) mice presenting established plaques with the iminosugar AMP-DNM for a period of 6 weeks. We showed that, considering the short-term treatment and the too advanced stage of the plaques, AMP-DNM did not promote any effect on the atherosclerotic lesions. In chapter V we reported on the positive effects of voluntarily wheel running in hyperlipidemic LDLR(-/-) mice. In this study we established that physical activity beneficially modulates cholesterol metabolism by enhancing its fecal excretion especially as bile acids and neutral sterols. This coincided with a reduced development of atherosclerosis similarly to what we observed with AMP-DNM treatment.

The study illustrated in chapter VI focuses on the evaluation of plasma chitotriosidase activity as marker for atherosclerotic burden in mice. Chitotriosidase is a chitinase secreted by lipid-laden macrophages and its activity is elevated in Gaucher patients. In man, chitotriosidase is expressed in the atherosclerotic lesion and its activity was shown to correlate with the disease. We found that also in mice chitotriosidase is expressed by macrophages in the lesion, but plasma enzyme activity did not reflect the lesion amount measured in the aortic sinus of the mice. AMP-DNM treatment consistently showed an impressive beneficial action on cholesterol homeostasis, characterized by increased fecal sterol loss. Ezetimibe, an inhibitor of cholesterol absorption is producing similar effects. In chapter VII, we compared AMP-DNM with Ezetimibe as combination treatment or as single-drug treatment. The combination treatment induced 2-fold increase in cholesterol output, suggesting that the effect of the two compounds is additional. Therefore AMP-DNM is acting by a different mechanism and is not affecting intestinal cholesterol absorption.

Atherosclerosis represents the vessel manifestation of the metabolic syndrome. In the liver non-alcoholic-steatop hepatitis (NASH) is the manifestation of the metabolic syndrome. Since this disease shares several similarities with atherosclerosis we decided to treat mice presenting NASH with AMP-DNM. We found (chapter VIII) that the treatment was able to recover almost completely the steatotic liver and to correct its fibrotic status. Treated livers presented similar lipids levels and fat accumulation of healthy mice. Insulin sensitivity was improved in the mice receiving AMP-DNM and inflammation was corrected. These impressive effects on hepatic lipids correlated with the observed stimulation of the beta-oxidation and the decreased lipogenesis.

In chapter IX we give an overview of the beneficial action of AMP-DNM on glucose homeostasis in several rodent models for the metabolic syndrome. Here
the role of glycosphingolipids in glucose homeostasis is discussed as well as possible future therapeutic strategies targeting glycosphingolipids metabolism.

In chapter X, the general outcomes of the different studies are discussed. Here the positive effects of AMP-DNM on cholesterol homeostasis, atherosclerosis and NASH are reviewed. Potential mechanism of action and future perspectives are listed.