PO127

Reducing glycosphingolipids restores insulin sensitivity in obese mice

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Pharmacological lowering of (glyco)sphingolipids has been demonstrated to be a novel approach to improve glycemic control. We have recently shown that lowering of glycosphingolipids (GSL) including GM3 using the iminosugar AMP-DNM improved glucose homeostasis.

We wanted to address how this improved glucose homeostasis was regulated by focussing on GLS lowering effects in adipose tissue and liver.

Leptin-deficient obese (LepOb) mice were fed a commercial chow diet (AM-II) with or without 100 mg AMP-DNM/kg bodyweight per day for 4 weeks. Adipose tissue was analysed at the level of gene expression and by immunohistochemistry studying adipogenesis and inflammation in detail. Liver was analysed at the level of gene expression and by oil red O staining, focussing on inflammation and lipogenic and glucose production pathways.

In adipose tissue, a critical mediator in obesity-induced insulin resistance, we demonstrated that AMP-DNM restored insulin signalling, improved adipogenesis (characterized by increased expression of peroxisome proliferator-activated receptor (PPAR)γ, insulin responsive glucose transporter (GLUT)-4 and adiponectin) and reduced pro-inflammatory adipose tissue macrophages (crown-like structures).

In liver lowering of GSL reduced hepatic steatosis in obese mice. First, it was observed that insulin signalling was restored in liver. Second, liver weight and fat content were reduced. Third, hepatic lipogenic and glucose production pathways were inhibited by AMP-DNM. Last, inflammation was reduced by AMP-DNM.

Lowering of GSL by inhibition of glucosylceramide biosynthesis not only improves adipocyte function and inflammation in adipose tissue, but also reduces hepatic steatosis in obese animals.

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PO128

Glycospingolipid synthesis inhibitor AMP-DNM and ezetimibe have a synergistic cholesterol lowering effect in mice

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High glycosphingolipid (GSL) levels have been associated with atherosclerosis and metabolic diseases in general. Previously, we have demonstrated in hyperlipidemic mice that inhibition of GSL synthesis with iminosugar N-(5′-adamantane-1′-yl-methoxy)-pentyl-1-deoxynojirimycin (AMP-DNM) increases fecal neutral sterol (FNS) output and prevents atherosclerosis. This increased sterol output has been attributed to increased biliary cholesterol secretion. However, an effect of AMP-DNM treatment on cholesterol absorption could not be ruled out. In this study we investigated how AMP-DNM treatment affects cholesterol transport in the liver and intestine. To this end we treated C57Bl/6 mice with AMP-DNM (100 mg/(day kg)) and/or with the inhibitor of cholesterol absorption ezetimibe (EZ; 10 mg/(day kg)). After 2 weeks, FNS output was 2-fold increased in mice treated with either EZ or AMP-DNM. Interestingly, a combined treatment of AMP-DNM and EZ increased FNS output 4-fold ($p < 0.05$). This suggests that AMP-DNM and EZ increase FNS output synergistically and via different mechanisms. We performed bile cannulations and intestine perfusions to determine how each treatment affects both biliary lipid secretion and the recently described transintestinal cholesterol efflux (TICE) pathway. Both cholesterol secretion pathways were unchanged upon treatment with EZ alone. In contrast, AMP-DNM treatment increased not only biliary cholesterol secretion (3-fold; $p < 0.001$), but also TICE (2-fold; $p < 0.05$).

These data show that inhibition of GSL synthesis by AMP-DNM in mice induces FNS excretion via biliary cholesterol secretion and TICE. Additional treatment with a cholesterol absorption inhibitor, further increases FNS excretion. Hence, AMP-DNM and EZ may have a synergistic cholesterol lowering effect.

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PO129

2-Hydroxyoleic but not 2-hydroxystearic acid reduces body weight, adipose tissue mass and hepatic SCD1 expression in diet-induced obese mice

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We recently showed that the not beta-metabolizable fatty acid, 2-hydroxyoleic acid, is able to reduce adipose tissue mass in lean Wistar rats (Vogler et al., 2008). The present work analyses the pharmacological effects of two natural (stearic acid (SA) and oleic acid (OA acid)) and two synthetic (2-hydroxystearic acid (2-OHSA) and 2-hydroxyoleic acid (2-OHOA)) C18 fatty acids in a diet-induced obese animal model. C57BL/6 mice were fed a diet containing 45 kcal% fat and treated orally for 7 days with 750 mg/(kg day) of the indicated fatty acids. Our results show that only 2-OHOA efficiently reduced body weight (−8.2%), food intake (−33.3%) and adipose tissue mass (−23.4%). OA and SA did not alter these parameters, whereas 2-OHSA even slightly increased them. A 44-day treatment with 400 mg/(kg day) of 2-OHOA demonstrated that its antiobese effect is drug tolerance-free, more potent if benchmarked against 10 mg/(kg day) sibutramine (−39.4% vs. −11.0%) and completely restoring physiological lean body weight while feeding a 60% high-fat diet. In liver tissue none of the carnitine palmitoyltransferase isoform levels (CPT1a, 1b, and 2) measured by qPCR were significantly altered by any of the compounds. Instead, 2-OHOA drastically reduced (−85%) transcription of hepatic stearoyl-CoA-desaturase 1 (SCD1), whereas 2-OHSA increased its mRNA level significantly (+72%). We suppose that inhibition of SCD1 transcription might be the molecular mechanism of 2-OHOA and that the structural requirements for fatty acids with such a