

ABSTRACTS

Abstracts for Oral Presentation:

OP3.

OXIDATIVE STRESS INDUCED BY INTERMITTENT HYPOXIA EXACERBATES LIPID ACCUMULATION AND INFLAMMATION IN A CELL MODEL OF NON-ALCOHOLIC STEATOHEPATITIS (NASH)

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Background/Aims: The prevalence of obstructive sleep apnea (OSA) is high in patients with non-alcoholic fatty liver disease (NAFLD) and NASH is a progressive hallmark of the pathogenesis of NAFLD. Chronic intermittent hypoxia is associated with recurrent episodes of oxygen desaturation and reoxygenation in OSA patients, leading to excessive production of reactive oxygen species (ROS). The causal link between OSA and NAFLD is not known and the mechanistic effect of intermittent hypoxia (IH) on the pathogenesis of NAFLD remains elusive. Here we tested the hypothesis that IH-induced oxidative stress aggravates lipid accumulation and inflammation induced by sodium palmitate in HepG2 cells.

Materials and Methods: HepG2 cells were treated with sodium palmitate or vehicle under normoxia (Nx) or IH condition for 72 hours in the presence or absence of a ROS scavenger MnTBAP. Cell viability was detected by MTT assay and intracellular lipid deposit was examined by oil red staining. Lipid peroxidation was measured by malondialdehyde (MDA) assay and levels of reactive oxygen species (ROS) were detected by CM-H2DCFDA staining. The expressions of pro-inflammatory cytokines (IL-1 β , TNF- α , IL-6), fatty acid uptake-associated genes (caveolin-1 and FATP5), fatty acid synthesis genes (SREBP1 and ACC1) and fatty acid β -oxidation gene ACOX were determined by real-time PCR.

Results: Results showed that sodium palmitate increased lipid deposit in the cells and it also decreased cell viability. The effect of sodium palmitate was more prominent in the group co-treated with hypoxia. Levels of MDA and ROS and the expressions of IL-1 β , TNF- α , IL-6 and caveolin-1, but not FATP5, were significantly increased in the palmitate- or hypoxia-treated group and were remarkably elevated in the co-treated group. These effects were abolished by MnTBAP treatment. In addition, levels of the expression of ACOX, SREBP1 and ACC1 were significantly lowered in the cells treated with palmitate or hypoxia and the expressions were much less in the co-treated group. Treatment of MnTBAP prevented the decreased expression of ACOX but had no effect on the SREBP1 and ACC1 expression.

Conclusion: IH-induced oxidative stress exacerbates lipid accumulation and inflammation induced by sodium palmitate in HepG2 cells, probably mediated by an increase in lipid uptake and a decrease in the fatty acid β -oxidation.

OP4.

ROLE OF PROSTAGLANDIN E RECEPTOR SUBTYPE 4 (EP4) IN THE REGULATION OF TRIGLYCERIDE METABOLISM

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Objectives: Hypertriglyceridemia is strongly associated with future risk of insulin resistance, diabetes and cardiovascular disease. Interestingly, it has been recently demonstrated that mice lacking cyclic AMP-responsive element-binding protein H (CREB-H) showed higher plasma triglyceride concentrations compared to wild-type mice. As an upstream stimulating factor of CREB-H, prostaglandin E receptor subtype 4 (EP4) may participate in the regulation of triglyceride metabolism. Thus, we tested whether or not deletion of EP4 influences triglyceride metabolism, and if so, to explore the underlying mechanisms.

Methods: EP4 wild-type and knockout mice were put on a high-fat diet (HFD) for thirty weeks and changes in plasma triglycerides were monitored. The impact of EP4 deletion on the ability to synthesize hepatic very low density lipoprotein (VLDL)-triglyceride (TG) and intestinal chylomicron (CM)-TG, as well as the ability to clear TG during HFD was examined. Lipoprotein lipase (LPL) activity and mRNA expression of LPL and CD36 in brown adipose tissue (BAT) were determined by fluorometric assay kit and quantitative polymerase chain reaction (Q-PCR), respectively.

Results: After thirty weeks of high-fat diet, EP4 knockout mice had a higher plasma TG level than wild-type mice. The deletion of EP4 did not influence hepatic VLDL-TG production or intestinal CM-TG synthesis but impaired

TG clearance rate. EP4 knockout mice had a decreased mRNA expression and activity of LPL in their BAT, suggesting impaired hydrolysis and uptake of triglycerides in this tissue. Moreover, EP4 knockout mice had a reduced expression of CD36 in BAT, which may indicate that the uptake of fatty acids is impaired.

Conclusions: Deletion of EP4 in high-fat fed mice resulted in hypertriglyceridemia. The hypertriglyceridemia that accompanies EP4 deficiency is the result of impaired TG clearance, attributed to reduced mRNA expression of LPL and CD36, and impaired LPL activity in BAT. The results indicate that EP4 plays a critical role in systemic lipid homeostasis.