proteins (APP) in body fluids when subjected to salt loading. We have demonstrated that rosuvastatin (RSV) reduces APP accumulation and prolongs survival of SHR-SR. Objective and Methods. The aim of the present study was to evaluate the mechanisms responsible for the renoprotective effect exerted by RSV in SHR-SR fed a high-salt diet. RSV (10 mg/kg/day; n=15) and vehicle-treated rats (n=15) were sacrificed when brain damage of the latter was detected by MRI. For comparison, baseline kidneys from SHR-SR (n=6) were collected at the start of the high-salt diet.

Results: By electron microscopy, we observed that vehicle-treated animals exhibited degenerative changes of podocytes, villous transformations, and focal detachment of cells from the glomerular basement membrane. These changes were reduced in rats given RSV. In comparison with the baseline rats, kidneys of the vehicle-treated rats presented massive inflammatory cell infiltration, accumulation of alpha-smooth muscle-positive myofibroblasts, collagen and fibrin deposition. Moreover, the renal tissue of these rats showed greater expression of PAI-1, tPA, uPA, MMP-2, and plasmin activity, but less MMP-9 expression.

Conclusions: RSV, without influencing plasma lipid levels, prevented all these modifications, indicating that this statin exerts a renoprotective effect in SHR-SR by preserving renal morphology, reducing inflammatory events, and modulating the “imbalance” in the plasminogen/plasmin and metalloproteinase systems.

Th-W48:7 PORCINE PLASMA PAF-ACETYLYHIDROLYASE: PHYSIOLOGY UPON DIET HYPERLIPIDEMIA. A SURROGATE MODEL OF HUMAN ATHEROSCLEROSIS.
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Objective: Plasma platelet-activating factor-acetylhydrolase (PAF-AH, LDL-PLA2 or PLA2G7) hydrolyzes PAF and PAF-like oxidized phospholipids is mainly produced by macrophages and is transported by plasma lipoproteins. We analysed the PAF-AH activity distribution in lipoproteins of hypercholesterolemic pigs and studied its correlation with blood parameters and the size and the composition of atherosclerotic plaques.

Methods and Results: In controls, PAF-AH activity was associated with HDL (70%) and LDL (30%); upon 12 wks of diet (4% cholesterol, 14% beef tallow and 2% hog bile) it raised in LDL (38%). In Blood, PAF-AH correlated with cholesterol and with oxidised LDL. In plagues, it correlated with lipids, macrophages and oxidised LDL, but not with plaque size. In pig, PAF-AH was 3-fold more active than in human plasma. To explore the molecular basis of such increase, the cDNA was cloned from pig macrophages showing that pig PAF-AH cDNA encodes a 430a protein and contains the conserved esterase triad (Ser274, Asp297, His351), the consensus binding sites for lipoproteins (Tyr115, Leu116, Tyr205) and is highly similar to bovine (84.2%) and human (80.5%). Kinetic studies of recombinant porcine and human PAF-AH showed different Km for PAF (8 vs 22 uM PAF) that may explain an observed 3-fold higher activity of pig PAF-AH.

Conclusions: Despite some differences with humans, pig might be a relevant surrogate model to study the involvement of PAF-AH in human atherosclerosis.

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Th-W48:8 THE IMMUNOSUPPRESSIVE EVEROLimus SIGNIFICANTLY PREVENTS ATHEROSCLEROSIS IN HYPERCHOLESTEROLEMIC LDLR-/- MICE
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The progression of atherosclerosis is characterized by cholesterol filled macrophages and the recruitment of effector T cells within the intima of the arterial wall. This is augmented by several inflammatory mediators and the proliferation of smooth muscle cells and fibroblasts. The mTOR inhibitor everolimus (Novartis Pharma AG) has been recently shown to inhibit growth factor promoted cell proliferation of hematopoietic and non hematopoietic cells and to reduce transplant vasculopathy in different animal models. The aim of our study was to investigate the effect of everolimus treatment (0, 0.05, 1.5 mg per kg bodyweight per day, n=20, n=15, n=12, respectively) on the development of atherosclerosis in male hypercholesterolemic LDLR-deficient mice. The drug was administered continuously by subcutaneous implanted osmotic minipumps and showed stable drug levels over the 12 week study period (36±2 and 42±25 µg/ml, 0.05 and 1.5 mg everolimus, respectively). Everolimus (1.5 mg per kg bw/day) did reduce significantly the size of atherosclerotic lesions at the brachiocephalic artery compared to the placebo treated mice (34±7±914 mm² vs. 59±9±744 mm², p<0.002). The strong antiatherosclerotic effect of everolimus was evident despite higher total plasma cholesterol in both treatment groups compared to placebo. The cellular plaque composition and pro- and antiinflammatory markers in the treated animals are presently under further investigation. We show for the first time that everolimus drastically reduces atherosclerosis despite high plasma cholesterol levels in the model of the LDLR-/- mouse.

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Th-W49 PHARMACOLOGY OF ARTERIAL DISEASE: NOVEL THERAPEUTIC APPROACHES (1ST PART)

Th-W49:1 BERBERINE IS A PROMISING NOVEL CHOLESTEROL-LOWERING DRUG WORKING THROUGH A UNIQUE MECHANISM DISTINCT FROM STATINS.
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Objective: Berberine is a benzyltetrahydroxyquinoline compound (MW of 371.8) isolated from Coptis chinensis. It has been extensively used in China as a non-prescription drug to treat diabetes for decades. Here we identify berberine as a novel cholesterol-lowering drug.

Methods and Results: Oral administration of berberine (1 gram per day) in 32 hypercholesterolaemic patients for 3 months reduced the serum cholesterol by 29%, triglyceride by 35%, and LDL-cholesterol by 25%. Liver enzymes were significantly reduced in the patients treated with berberine and kidney function was without change. Treatment of hyperlipidemic hamsters with BBR reduced serum cholesterol and LDL-cholesterol by 40% and 42% with a 3.5-fold and a 2.6-fold increases in hepatic LDLR mRNA and protein. Lipid storage in the liver was largely reduced in the hyperlipidemic hamsters treated with berberine. The upregulation of LDLR in the liver is associated with the upregulation of the LDL receptor mRNA by Herbal Medicine Berberine. Through a Unique Mechanism Distinct From Statins.

Conclusions: These findings discover BBR as a novel hypolipidemic drug with a unique working mechanism different from statins.

References

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