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ABSTRACTS
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PO6-46 ANTIATHEROGENIC EFFECTS OF CILOSTAZOL AND PROBUCOL ALONE, AND IN COMBINATION IN LOW DENSITY LIPOPROTEIN RECEPTOR-DEFICIENT MICE FED A HIGH-FAT DIET

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Background and aims: Cilostazol, an antiplatelet drug, and probucol, a cholesterol-lowering drug, are reported to ameliorate atherosclerosis in animal models. However, their combined effect on atherosclerosis is unclear. We therefore evaluated their combined effect on atherosclerotic lesions in LDL receptor-deficient mice.

Methods: Male LDL receptor-deficient mice were fed a high fat diet with or without cilostazol alone, probucol alone, or with cilostazol and probucol in combination, for 8 weeks. Body weight and plasma lipid levels were measured before and during treatment. At the end of treatment, the size distribution of plasma lipoproteins was analyzed by HPLC and then plasma HDL cholesterol levels and en face aortic atherosclerotic lesion areas were measured.

Results: Probucol alone significantly decreased both total cholesterol and HDL cholesterol, while cilostazol alone did not decrease total cholesterol but significantly increased HDL cholesterol. Both cilostazol alone and probucol alone significantly decreased atherosclerotic lesion areas, and their combined administration showed more significant decreases than when each drug was administered singly.

Conclusion: The combination of cilostazol and probucol was more effective in preventing atherosclerotic lesion formation than the administration of each drug alone; this may provide us with a new strategy for treating atherosclerosis.

PO6-47 ATHEROGENESIS, PANCREATITIS AND BRAIN DYSFUNCTION IN LPL DEFICIENT MICE WITH SEVERE HYPERTRIGLYCERIDEMIA

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Backgound and Aim: Mice of homozygous lipoprotein lipase (LPL) gene deficiency could be rescued from neonatal lethality by somatic gene transfer of a beneficial mutant. These mice developed severe hypertriglyceridemia, which mimics that of human mutations in LPL gene.

Methods and results: At age over 15 months unexpected spontaneous atherosclerosis was detected in these mice and high levels of oxidative products in plasma and chylomicrons (CM) were accumulated. The CM from old mice have strong effect on activation of endothelial cells as assessed by macrophage adhesion and VCAM1/MCP1 up-regulation. Similar to LPL deficient patients, these mice have increased susceptibility to acute pancreatitis. In pancreatic acinar cells from wild type mice addition of CM caused stimulation of amylase release, irreversible Ca^{2+} release and cell damage. This effect was decreased in the presence of the lipase inhibitor orlistat and was increased in the presence of the secretagogue CCK that also led to generation of FFA from CM.

After discovery of learning and memory deficit in these mice electron microscopy revealed the significant decrease of pre-synaptic vesicles in hippocampi. Furthermore, synaptophysin, one of the most important pre-synaptic marker, also reduced significantly.

Conclusions: The alterations in multi-organs suggested that severe HTG might exert pathological effects via certain common mechanisms to induce organ injury, which will provide new insights into lipid-related cellular stress.

PO6-48 THE BIOCHEMICAL AND CARDIOVASCULAR CONSEQUENCES OF LCAT DEFICIENCY

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We have recently identified 14 Italian families with LCAT deficiency, carrying 19 different mutations in the LCAT gene. All carriers of two mutant LCAT alleles (n=17) had remarkably low plasma HDL-C, apoA-I, and apoA-II levels, associated with multiple alterations in HDL structure and particle distribution, with a selective depletion of LpAI:A-II particles, a predominance of small, pre-beta-migrating HDL and a complete lack of HDL2. Unesterified cholesterol, the unesterified/total cholesterol ratio, VLDL-cholesterol, and triglycerides were significantly elevated, whereas apoB was significantly lower compared to controls. Twenty-three out of 44 carriers of one mutant LCAT allele (53%) had a low plasma HDL-C; the average plasma HDL-C and apoA-I levels were significantly lower than in controls. Plasma LCAT activity was also significantly lower than in controls. Despite the atherogenic profile, only one of the 17 carriers of two mutant LCAT alleles, a 71 y.o. man with elevated LDL-C, hypertension, and diabetes, presented with premature coronary artery disease. The evaluation of carotid intima-media thickness (IMT) showed that carriers of two mutant LCAT alleles have IMT values comparable to age-sex matched controls, despite the severe hypoalphalipoproteinemia. Carriers of one mutant LCAT allele have widely distributed IMT values, showing on average IMT values comparable to controls. In a large series of subjects carrying mutations in the LCAT gene, the inheritance of a mutated LCAT genotype causes a gene-dose-dependent alteration in the plasma lipid/lipoprotein profile. No premature cardiovascular disease and no increase in carotid IMT was observed, despite the hypoalphalipoproteinemia, in the Italian LCAT deficient subjects.

PO6-49 TRANS INTESTINAL CHOLESTEROL EFFLUX PATHWAY IS REDUCED IN APOE KNOCKOUT MICE

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The Trans Intestinal Cholesterol Efflux (TICE) pathway contributes for a substantial amount to body neutral sterol output and provides an attractive target to increase the rate of CH excretion. In contrast to the reverse cholesterol transport pathway via the hepatobiliary route, this pathway does not seem to be HDL dependent based on experiments with SRB1-/- mice. Interestingly, induced TICE after feeding mice either a high fat containing diet or PPARδ agonist GW610742 correlated with elevated serum levels of LDL.

To discern whether apoE containing lipoproteins may be involved, we intravenously injected chylomicron-mimicking TG-rich emulsion particles containing either 3H-cholesteryl oleate (3H-CO) or cholesteryl oleyl ether (3H-COEth), which is resistant to intracellular hydrolysis, in WT and apoE-/- mice. Two hours after injection the proximal small intestine (10 cm) was canulated and perfused for 90 min with buffer containing taurocholate/lecithin (10mM:2mM).

In mice injected with 3H-COEth no radioactivity could be detected in intestinal mucosa and perfusate. Apparently, no direct uptake or translocation of these injected TG-rich lipoproteins took place. In ApoE-/- mice injected with 3H-CO, the specific CH activity in mucosa of the perfused intestine and the perfusate was only 50% of that found in WT mice. Interestingly, in WT mice this specific CH activity in perfusate was 4-fold higher than that found in the mucosa of the perfused intestine suggesting highly specific trafficking of CH from serum lipoproteins across the enterocyte.

In conclusion, our data suggest that LDL is involved in the delivery of CH and contribute to the rate of TICE.

PO6-50 RECOMBINANT PAF-ACETYLHYDROLASE ENHANCES THE CHOLESTEROL EFFLUX FROM MACROPHAGES INDUCED BY RECONSTITUTED HIGH DENSITY LIPOPROTEIN OR APOLIPOPROTEIN A-I

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Background and aim: High-density lipoprotein (HDL) exhibits important antiatherogenic activities, however the role of each HDL component in its biological effects remains to be established. One of the HDL components is platelet-activating factor acetylhydrolase (PAF-AH), alternatively named as lipoprotein-associated phospholipase A2 (Lp-PLA2), an enzyme that degrades PAF and oxidized phospholipids. We studied the possible role of recombinant PAF-AH (rPAF-AH) on cholesterol efflux induced by apolipoprotein A-I (apoA-I) or reconstituted HDL particles (recHDL) in mouse J774 macrophages.