then increased at 24 h along with an increase in FXR. Geranylgeraniol abolished the effects of pitavastatin on apo A-I, PPARα, and FXR, but enhanced the induction of CYP7A1 mRNA by pitavastatin, suggesting the existence of factors that regulate CYP7A1 in the non-sterol/geranylgeranyl diphosphate (GGpp) pathway. However, the inhibition of Rho-kinase by Y27632 enhanced the effects of pitavastatin on the induction of mRNA levels of apo A-I, PPARα, and FXR, but not that of CYP7A1, suggesting that PPARα may not be a major factor that regulates CYP7A1.
Conclusions: Pitavastatin increases CYP7A1 mRNA levels in HepG2 cells, suggesting that increased conversion of cholesterol into bile acids may be a mechanism for the potent LDL-C-lowering effects of pitavastatin. Increased CYP7A1 mRNA levels by pitavastatin are the net effect of the induction of CYP7A1 by the inhibition of cholesterol synthesis and the suppression of CYP7A1 by inhibition of the non-sterol /GGpp pathway.

1083-191 Biphasic Regulation of STAT1alpha Expression in Vascular Smooth Muscle Cells by Oxidized Low-Density Lipoprotein

Koichi Ono, Sergiy Sukhanov, Yao Hua Song, Patrick Delafontaine, Tulane University School of Medicine, New Orleans, LA

Atherosclerosis is a pro-inflammatory disease involving the effects of many cytokines and growth factors, that signal via distinct pathways, such as the janus kinases (JAKs) and signal transducers and activators of transcription (STAT). Oxidized LDL (OxLDL) is critical for atherosclerotic plaque generation and progression. To examine potential regulation of STAT1a by OxLDL in vascular smooth muscle cells (VSMC), we incubated VSMC with 0-100 microg/ml OxLDL or native LDL (nLDL) and measured STAT1a expression by real-time PCR and Western blotting. OxLDL, but not nLDL, dose-dependently increased STAT1a expression at 3h (51+-1% mRNA increase; 23+-1% protein increase n=3, p<0.01), but markedly reduced STAT1a expression at later time points (89.7+-6.7% decrease in protein levels at 9hr). To determine intracellular signaling pathways mediating OxLDL effects on STAT1a expression, we studied the role of candidate proteins implicated in OxLDL signaling. OxLDL components are high-affinity ligands for PPAR-gamma (PPAR-g), but the effect of OxLDL was not blocked by the PPAR-g inhibitor PGF2a and the synthetic PPAR-g ligand ciglitazone did not regulate STAT1a expression. Furthermore, inhibition of the p38 MAPK pathway (SB203580) or p42/44 MAPK pathway (PD98059) did not modify OxLDL effects, indicating that the ability of OxLDL to regulate STAT1a was not mediated via a p38 or p42/44 MAPK dependent pathway. Likewise, inhibition of the ubiquitin/proteasome pathway (MG132) did not blunt OxLDL regulation of STAT1a. However, 40nM Fucoidan (a scavenger receptor A inhibitor) and Anti-CD36 antibody (a scavenger receptor B inhibitor) markedly blocked OxLDL regulation of STAT1a expression (64%, 71% inhibition, respectively). Furthermore, the water-soluble Vitamine E derivative, Trolox, completely inhibited OxLDL regulation of STAT1a. In conclusion, OxLDL causes biphasic regulation of VSMC STAT1a expression via a PPAR-g, p38 MAPK, p42/44 MARK-independent and redox-dependent pathway that is mediated via scavenger receptors type A and B. These findings have important implications for understanding cellular signaling events regulated by OxLDL, and hence mechanism of atherogenesis.

1083-192 Large Oligomeric Grape Skin Polyphenolics Are Most Effective as Antioxidants and Antiplatelet Agents

Mark R. Beahm, Dhanansayan Shanmuganayagam, Areyl D. Goff, Christian G. Krueger, Jess D. Reed, John D. Folts, University of Wisconsin Medical School, Madison, WI, University of Wisconsin - Madison, Madison, WI

Background: Grape skin polyphenolics (PP) exhibit antioxidant and antiplatelet effects, which may reduce the risk of CVD in individuals consuming them. As these PP are chemically diverse, it is unknown which classes of PP are most effective. We hypothesized that different classes of PP will be differently effective as antioxidants and antiplatelet agents.
Methods: We fractionated a grape skin extract into 6 distinct PP fractions (F1-6; normalized to 5μM gallic acid equivalents of redox potential) using multiple solvent elutions through a Sephadex LH-20 column. F1-6 were characterized using HPLC and MALDI-TOF mass spectrometry. Antioxidant effect was determined by measuring the ability of F 1-6 and ascorbate (control) to extend the lag time to Cu^{2+}-induced oxidation of LDL (n=5): 1) by direct incubation (DI) with the LDL, and 2) by incubating LDL with the compounds and then washing the LDL to remove unbound compounds (TW). Antiplatelet effect was measured using collagen induced whole blood platelet aggregation (PA).
Results: F1-3 contained oligosaccharides, hydroxycinnamic acids, anthocyanins, flavanols and low-MW polygalloyl polyflavan-3-ols (PGPF). F4-6 contained PGPF with 4-8, 5-10, and 6-16 degrees of polymerization, respectively. In DI study, F1-3 extended lag time to LDL oxidation by 64±4%, 156±3%, 147±4%, but failed to retain this effect in the TW study. F1-2 had no effect on PA, however F3 significantly stimulated PA by 31±6%. F4-6 extended DI lag time by 158±1%, 113±7%, and 144±2% and retained 80%, 100%, and 100% of this effect in TW, respectively. F4-6 significantly inhibited PA by 55±14%, 98±0%, and 99±0%, respectively.
Conclusions: F5-6, containing PGPF with 5-16 degrees of polymerization, were most effective as antioxidants and antiplatelet agents. They were also most effective at binding LDL. This suggests that large MW PGPF may be primarily responsible for the beneficial effects of grape skin PP. Conversely, certain PP, such as F3, which stimulated PA, may have undesirable effects on CVD risk factors. Careful study of various classes of PP in a diet may be crucial in determining the overall effect of the PP on CVD.

POSTER SESSION

1084

Lipid Intervention: Statins

Monday, March 08, 2004, Noon-2:00 p.m.
Morial Convention Center, Hall G
Presentation Hour: 1:00 p.m.-2:00 p.m.

1084-168 Multidrug Resistance-1 Gene Polymorphisms Influence the Response to Atorvastatin Treatment in a Gender Specific Manner

Kouji Kajinami, Noboru Takekoshi, Margaret E. Brousseau, Jose M. Ordovas, Ernst J. Schaefer, Kanazawa Medical University, Uchinada, Japan, Tufts University, Boston, MA

*Background:*The mechanisms responsible for interindividual variations in response to statin therapy remain uncertain. Proteins involved in the drug metabolizing system may influence the plasma concentration of statins, and ultimately, plasma lipid levels. *Objectives:*To test the hypothesis that genetic variation in the multidrug resistance-1 (*MDR1*) gene, which encodes for P-glycoprotein that serves as a drug efflux pump, influences the plasma lipid response to statin therapy. *Methods*: Two prevalent *MDR1* polymorphisms (G2677T/A and C3435T) were examined in 344 hypercholesterolemic patients treated with atorvastatin 10mg. *Results:* In women, homozygosity for the 3435C wild type allele was significantly and independently associated with smaller reductions of low-density lipoprotein (LDL) cholesterol (-35±10% vs. -39±8%, p=0.023), but with larger increases of high-density lipoprotein (HDL) cholesterol (+12 ±14% vs. +7±11%, p=0.023), when compared to subjects carrying at least one variant allele. The G2677T/A polymorphism was not associated with treatment response. In women, homozygotes for the wild type haplotype (2677G and 3435C) experienced significantly smaller reductions in LDL cholesterol levels, as compared to subjects carrying the variant haplotype. Furthermore, in women, the increase in HDL cholesterol seen with atorvastatin treatment diminished in accordance with the number of variant haplotypes in a gene-dose dependent manner (p=0.042 for trend). *Conclusions:* In patients with hypercholesterolemia, the *MDR1* C3435T polymorphism is significantly and independently associated with the response to atorvastatin in a gender-specific manner. Haplotype analysis enabled us to identify a subgroup that showed a striking response to treatment, which was not defined by single polymorphism analysis.

1084-169 Efficacy and Safety of Ezetimibe Coadministered With Simvastatin Versus Simvastatin Alone in Thiazolidinedione-Treated Patients With Type 2 Diabetes Mellitus

Linda Gaudiani, Andrew Lewin, Luigi Meneghini, Inna Perevozskaya, Jonathan Tobert, Diane Plotkin, Yale Mitchel, Sukrut Shah, Marin Endocrine Associates, Greenbrae, CA, Merck Research Laboratories, Rahway, NJ

Background: In patients with type 2 diabetes mellitus (T2DM) who are at high risk of coronary heart disease, combination therapy is often required to regulate glucose metabolism and to attain aggressive target levels of low-density lipoprotein cholesterol (LDL-C). The marketed thiazolidinediones (TZD) improve glycemic control and have minimal effects on blood lipids. Ezetimibe (EZE), a novel intestinal cholesterol absorption inhibitor, has a complementary mechanism of action to statins, which inhibit hepatic cholesterol synthesis. We compared the safety and lipid-modifying effects of adding EZE to simvastatin (SIMVA) versus doubling the dose of SIMVA in TZD-treated T2DM patients.
Methods: This was a randomized, double-blind, parallel group, multicenter study in T2DM patients (HbA1c ≤9%), 30-75 years, with LDL-C ≥ 100 mg/dL, and stabilized on a TZD for ≥ 3 months. Patients received open-label SIMVA 20 mg/d for at least 6 wks, and then were randomized in a double-blind manner to either EZE 10 mg/d (n=104) or SIMVA 20 mg/d (n=110), added to ongoing open-label SIMVA 20 mg/d for 24 weeks. Patients were stratified according to TZD type and dose (pioglitazone 15-30 vs 45 mg/d; rosiglitazone 2-4 vs 8 mg/d).
Results: After 6 wks of open-label SIMVA 20 mg, mean (SD) LDL-C values for the EZE+SIMVA and SIMVA only groups, respectively, were 93.7 (28.5) and 91.4 (24.3) mg/dL. LDL-C was reduced more (p<0.001) by adding EZE 10 mg to SIMVA 20 mg (-20.8%) than by doubling the dose of SIMVA to 40 mg (-0.3%). EZE+SIMVA 20 mg also produced significant reductions in non-HDL-C (-20.0%; p<0.001), VLDL-C (-16.3%; p<0.001), and apo B (-14.1%; p<0.001). Triglyceride and HDL-C were not changed significantly by either treatment beyond the levels achieved on open-label SIMVA 20 mg. There were no significant differences in safety parameters between the treatment groups.
Conclusions: Coadministration of EZE with SIMVA, a treatment strategy that affects cholesterol synthesis and absorption, provides greater efficacy than doubling the dose of SIMVA in T2DM patients with mildly elevated LDL-C. The combination of EZE plus SIMVA is a well-tolerated and efficacious treatment option for lowering LDL-C in T2DM patients taking TZDs.

1084-171 Initial Response to Statin Therapy Predicts Response to Dose Titration

Mateen Akhtar, Kirk L. Peterson, Paul S. Phillips, Ori Ben-Yehuda, University of California, San Diego, La Jolla, CA

Background: NCEP guidelines recommend dose titration in patients who have not achieved LDL goal at starting dose. We hypothesized that initial response to statin therapy would predict response to dose titration.
Methods: Retrospective study of 76 adult patients with CAD who met criteria for statin therapy per ATP III guidelines and were treated at initial statin dose followed by dose titra-