Results: Fifty-six patients (31.6%) had elevated cTnl > 1.0 ng/mL at the time of PE diagnosis. Patients with elevated cTnl were older (p<0.01) and had higher incidence of malignancy (p=0.006) but no increased prevalence of prior MI or CAD (p=0.62). Elevated cTnl was associated with adverse outcomes including 30-d mortality (p<0.01) (Table 1). After adjusting for possible confounders, the association of cTnl with adverse outcomes remained.

Conclusions: In the setting of acute PE, elevated cTnl is associated with increased 30-d mortality and adverse cardiopulmonary/ hemodynamic outcomes. Elevated cTnl may identify high-risk patients with PE more likely to benefit from aggressive therapies such as thrombolytics.

Poster Session

1033 Cardiac Signaling Pathways

Sunday, March 17, 2002, Noon-2:00 p.m.
Georgia World Congress Center, Hall G
Presentation Hour: Noon-1:00 p.m.

1033-90 The Angiotensin II Type I Receptor Associated Protein ATRAP Is a Transmembrane Protein and Negative Modulator of Angiotensin II Signaling

Marco A. Lopez-Ilasaca, Victor J. Dzau, Brigham & Women’s Hospital, Boston, Massachusetts; Harvard Medical School, Boston, Massachusetts.

AT1 receptor-associated protein (ATRAP) was identified by our group in a yeast two-hybrid screen for proteins that bound to the carboxyl-terminal cytoplasmic domain of the Angiotensin II type 1 receptor (AT1). In this work we characterize ATRAP as a transmembrane protein, localized in the endoplasmic reticulum and plasma membrane that functions as a negative modulator of Angiotensin II-induced signal transduction. Endogenous and transfected ATRAP cDNA shows a particular distribution; hydrophobicity analysis of the primary structure of ATRAP reveals the presence of three transmembrane domains at the amino terminal of the protein and a hydrophilic cytoplasmic carboxyl-terminal tail. Deletion of the N-terminal transmembrane domains leads to a diffuse cytoplasmic distribution of the protein. Electron microscopy reveals the presence of ATRAP in prominent perinuclear vesicle clusters, whereas the distribution of the protein in the endoplasmic reticulum and plasma membranes is not altered.

1033-91 Mechanisms of Thromboxane A2 Associated Apoptosis in Adult Cardiac Myocytes: Role of Protein Kinase C Zeta Mediated Downregulation of Akt Activity


Background: Apoptosis (Ap) is seen in myocardium exposed to acute ischemic insults and Apo may be in part mediated by increased thromboxane A2 (TXA2) level. We investigated the role of protein kinase C (PKC) in Apo induced by TXA. Methods: Adult rat ventricular myocytes (ARVM) were cultured for 48 h before pharmacological interventions. The involvement of PKC was measured with both translocation and immune complex kinase assay. Akt activity was measured with both translocation and immune complex kinase assay. The extent of apoptosis was assessed with TUNEL and DNA ladder assay. Results: Treatment with a TXA mimic, IBOP for 24 h induced Apo in ARVM in a dose-dependent fashion (n=0.03) in 100 nM IBOP (P<0.15 vs. controls, P<0.05). The Apo by TXA was completely inhibited by a TXA receptor specific inhibitor SQ29548. TXA stimulation resulted in membrane translocation of PKC at 3 min and 1 h stimulation, but not PKCz, βII, and δ. The ioenzyme specific activity of PKCz was confirmed by an immune complex kinase assay. The activation of PKCz by TXA was also associated with reduction of Akt activity. A cell permeable PKCz specific pseudosubstrate peptide (PSP; a gift from Dr. Moehly-Rosen, Stanford University, CA) inhibited apoptosis by TXA at a dose which inhibited TXA-mediated increase in PKCz activity (1 μM). PSP also inhibited Akt inhibition by TXA. The

1033-92 Stimulation of Cyclic AMP Synthesis by Combined Overexpression of the Nucleoside Diphosphate Kinase NM23-H2 and the Alpha-Subunit of Ga Proteins

Feravdoon Niroomand, Hans-Joerg Hippe, Susanne Lutz, Katrin Knorr, Matthias Meyborg, University of Heidelberg, Heidelberg, Germany.

Background: Ga proteins are mediators of signaling pathways that are implicated in the development of cardiac hypertrophy and dilation. We have recently suggested a receptor-independent mechanism of Ga protein activation by a membrane-associated nucleoside diphosphate kinase (NDPK). In sarcolemmal membranes from failing human hearts, the level and activity of NDPK were elevated three-fold, leading to a 50–75% inhibition of cAMP-synthesis. This finding could reflect activation of the likewise increased Ga proteins. To prove the interaction of NDPK with a Ga protein, we transfected cells with genes encoding for NDPK and the alpha-subunit of the stimulatory Ga protein Gsa. Methods: Immunoprecipitated, cell-derived proteins from Hela cells stably transfected with the NDPK-gene NM23-H2. Overexpression of Gsa was induced with a recombinant adenovirus. Intracellular cAMP and adenylyl cyclase activity (AC), NDPK-activity, Gsa and Gsa in membranes were determined. Results: Overexpression of Gsa led to an increase in cAMP synthesis in all cell clones, despite the presence of the inverse agonist propranolol. This increase was strictly proportional to the level of NDPK activity in different cell clones. In cells with a 2-fold overexpression of NDPK and a 10-fold overexpression of Gsa, intracellular cAMP was increased 200-fold compared to control cells. Stable transfection of the cells with a catalytically inactive NDPK did not increase cAMP-synthesis. Intracellular nucleotide concentrations were not influenced by the overexpression of NDPK. In crude membranes from these cells, basal, G protein independent AC activity was similar in all clones. However, in cells overexpressing Gsa and NDPK, AC activity in the presence of GDP was increased proportionally to the level of NDPK activity, in conclusion, these results demonstrate for the first time a functional interaction of NDPK with a G protein in an intact cell.

1033-93 Antioxidant Vitamins C and E Administration in Smokers: Effects on Endothelial Function and Serum Levels of Soluble Intercellular Adhesion Molecule-1, Soluble Vascular Cell Adhesion Molecule, and Lipid Hydroperoxides

Dimitris Tousoulis, Charalampos Antoniadou, Marina Toutouza, Costas Toutouzas, Kyriakos Mariou, George Goumas, Athanasias Tirakas, Costas Toutouzas, Christodoulos Stefanidis, Pavlos Toutouzas, Cardiology Unit and Hipppokration Hospital, Athens University Medical School, Athens, Greece.

Background: Serum levels of soluble vascular cell adhesion molecule (sVCAM-1) and soluble intercellular adhesion molecule (sICAM-1), as well as lipid hydroperoxides (LPO) (marker of lipid peroxidation), are implicated in the pathogenesis of atherosclerosis. Purpose of this study is to investigate the effects of combined administration of antioxidant vitamins C and E on endothelial function, and serum levels of sICAM-1, sVCAM-1 and LPO in chronic smokers.

Methods: 36 healthy young smokers (20 males 16 females aged 36±2 years) were enrolled in this double blind placebo controlled study. Subjects were divided into 4 groups receiving vitamin C 2g/day (n=10) (group A), vitamin C 2g/day and vitamin E 400IU/day (n=11) (group B), vitamin C 2g/day and vitamin E 800IU/day (n=8) (group C) or placebo (n=6) (group D), for 4 weeks. Forearm blood flow was measured using venous occlusion strain gauge plethysmography. Endothelium dependent flow mediated vasodilation (FMD) was expressed as the % change from baseline to post reactive hyperemia blood flow. Endothelium independent % change flow (NTR%) was assessed after sublingual nitroglycerin administration. Plasma levels of sVCAM1, and sICAM1 were determined by enzyme linked immunosorbent assay, while LPO was determined using a spectrophotometric assay.

Conclusions: Chronic administration of vitamin C (2g/day) combined with vitamin E (800IU/day), reduces blood levels of sVCAM-1 and sICAM-1, improves endothelial function and reduces lipid peroxidation in healthy young smokers. These findings may have therapeutic implications in chronic smokers.