S-II-5

MOLECULAR MECHANISMS OF CARDIOPROTECTION BY A NOVEL GRAPE SEED PROANTHOCYANIDIN EXTRACT

Debasis Bagchi, Harry G. Preuss, and Dipak K. Das

Creighton University School of Pharmacy & Allied Health Professions, Omaha, NE 68178.
Email: debsis@creighton.edu Fax: +1 402 280-1883

Free radicals and oxidative stress play a crucial role in the pathophysiology of a broad spectrum of cardiovascular diseases including congestive heart failure, valvular heart disease, cardiomyopathy, hypertrophy, atherosclerosis and ischemic heart disease. We have demonstrated that IH636 proanthocyanidin extract (GSPE) provides excellent protection against free radicals in both *in vitro* and *in vivo* models, and exhibits significantly better efficacy as compared to vitamins C, E and β-carotene. A series of studies were conducted to assess the cardioprotective ability of GSPE. GSPE was administered orally (100 mg/kg/day) supplemented with regular diet for 3 weeks to a group of rats, while the other group was given the regular diet only. Then the rats were sacrificed, hearts excised and perfused *via* Langendorff mode. Hearts were made globally ischemic for 30 min followed by 2 hr of reperfusion. Aortic and coronary flow, developed pressure and left ventricular function, infarct size, malondialdehyde formation in the heart perfusate, and contractile function by ESR technique were monitored. Cardiomyocyte apoptosis was examined by terminal deoxynucleotidyltransferase-mediated dUTP nick end labeling (TUNEL) staining in conjunction with an antibody against myocin heavy chain to specifically detect apoptotic myocytes. Induction of JNK-1 and c-fos proteins was studied by Western blot analysis using respective antibodies followed by densitometric scanning, GSPE significantly improved left ventricular function, post-ischemic contractile recovery, myocardial ischemia-reperfusion-induced oxidative stress and infarction and reduced the appearance of apoptotic cardiomyocytes in the ischemic reperfused hearts. The novel cardioprotective protective properties of GSPE may be at least partially attributed to its ability to block anti-death signal through the inhibition of proapoptotic transcription factor and gene, JNK-1 and c-Jun. In another set of experiment, we have

assessed Doxorubicin-induced cardiotoxicity in mice. GSPE (100 mg/kg p.o. for 7 days) pretreatment significantly inhibited doxorubicin (20 mg/kg i.p. 48 hr)-induced DNA fragmentation, serum chemistry (ALT, CK and BUN) and histopathological changes. Concentration-dependent efficacy of GSPE was also assessed in a hamster atherosclerosis model. Hamsters exhibit a similar lipid profile to hypercholesterolemic humans when fed a hypercholesterolemic diet of 0.2% cholesterol and 10% coconut oil and develop foam cells, a biomarker of early stage of atherosclerosis. Approximately 49% and 63% reduction in foam cells were observed following supplementation of 50 and 100 mg GSPE/kg to the hamsters. Recently, a human clinical trial was conducted in hypercholesterolemic subjects. GSPE supplementation significantly reduced oxidized LDL in human subjects, a biomarker of cardiovascular diseases. These results demonstrate that GSPE may serve as a potential therapeutic tool in promoting cardiovascular health by a number of novel cytoprotective mechanisms.