SESSION 7

TRACE ELEMENTS AND MINERALS IN CARDIOVASCULAR DISEASES, DIABETES AND METABOLIC SYNDROME

MAGNESIUM L-ASPARTATE CORRECTS FUNCTIONAL HEART RESERVES IMPAIRED DUE TO MAGNESIUM DEFICIENCY

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Magnesium (Mg) is well-known to be essential for blood pressure level regulation, prevention of vessel wall injury and atherosclerosis and controlling of impulse conduction in heart. On the other hand, data about magnesium effectiveness for chronic heart insufficiency are controversial. The purpose of the study was to evaluate functional heart reserves in Mg-deficient rats before and after supplementation with Mg L-aspartate. Mg deficiency was induced in 72 rats fed with Mg-deficient diet (Mg content < 15 mg/kg) and demineralised water for 7 weeks. The Mg-deficient diet contained (per kg of diet) 200 g of casein with Mg content < 5 mg/kg, 3 g of DL-methionine, 50 g maize oil, 700 g of potato starch with Mg content < 20 mg/kg, 35 g of AIN-76 mineral mix without MgO, 10 g of ICN vitamin mix and 2 g of choline bitartrate. For the same time 21 control (intact) rats were fed with a basal control diet (Mg content > 0.5 g/kg). Afterwards, Mg L-aspartate, its combination with pyridoxine and Mg lactate with pyridoxine (50 mg Mg/kg body weight) were orally introduced to magnesium-deficient rats through gastric tube for the time period of 3 weeks. To estimate myocardial function, left ventricular pressure, rates of contractility and relaxation, heart rate, systolic and diastolic blood pressure were measured in response to volume loaded test, adrenoreactivity test and maximal isometric loaded test. Mg deficiency was found to be associated with reduction of intraerythrocytic (0.92 ± 0.06 mmol/l vs. 2.01 ± 0.05, $p < 0.001$) Mg level in comparison with control rats. Volume loaded test resulted in increase of left ventricular pressure 2.6 times less, increase of rate of contractility 1.7 times less and increase of rate of relaxation 2.6 times less in comparison with control group ($p < 0.05$). Epinephrine was shown to increase left ventricular pressure, rates of myocardial contractility and relaxation 2.3, 2.25, 2.6 times less as compared to control group ($p < 0.05$). Ascending part of aorta's arch cross-clamping caused an increase of left ventricular pressure, rates of myocardial contractility and relaxation 1.7, 2, 2.12 times less than in control group ($p < 0.05$). Thus cardiac failure in Mg deficient rats might be evidence of reduced ability of myocardium to accommodate itself to increasing load. After 21-day treatment with Mg salts hemodynamic parameters in all studied tests were comparable with parameters in intact rats. Growth of integral index of structure functioning in group administered Mg L-aspartate in combination with pyridoxine increases significantly higher in comparison with Mg lactate in combination with pyridoxine.

PROTECTIVE ROLE OF SELENIM IN DIABETES-INDUCED CARDIOVASCULAR DYSFUNCTION: EXPERIMENTAL STUDIES

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Diabetes mellitus is a major risk factor for multiple cardiovascular complications resulted from multiple parameters including glucotoxicity, lipotoxicity, fibrosis and mitochondrial uncoupling. Oxidative stress arises from an imbalance between the production of ROS and the biological system's ability to readily detoxify the reactive intermediates. Several studies have reported beneficial effects of antioxidant agents, including selenium and other trace elements, against the cardiovascular system dysfunction as the consequences of diabetes. Antioxidants act through one of 3 mechanisms to prevent oxidant-induced cell damages. They can reduce the generation of ROS, scavenge ROS, or interfere with ROS-induced alterations. In addition, it has been shown that matrix metalloproteinases (MMPs) are activated by ROS and can function in the cytosol of the cell by proteolytic cleavage of susceptible intracellular targets including contractile proteins of heart and vessels. Since selenium compounds can restore some metabolic parameters and structural alterations of diabetic tissues, we studied the effect of selenium treatment of diabetic rat heart and vessel functions. Diabetes was induced by streptozotocin (50 mg/kg body weight) and rats were then treated with sodium selenate (15 μmol/kg body weight/day) for 4 weeks. Sodium selenate treatment of diabetic rats improved markedly diabetes-induced prolongation in action potential duration and depression in mechanical activity of the heart via preserving inhibited K^+-currents and Ca^{2+} homeostasis. Diabetes-induced both receptor- and smooth muscle-mediated dysfunction of vasculature are also normalized in the treated rats. Our biochemical data showed that selenium treatment induced a well-tuned, balanced and responsive antioxidant defence system in the diabetes-induced increased oxidative stress in different types of tissues. In addition, this treatment restored diabetes-induced increased levels of oxidized glutathione, protein-thiol oxidation, PKC, and cAMP production as well as altered MMP-regulation in the tissues of cardiovascular system. Such an observation provides evidence for potential therapeutic usage of selenium compounds for the amelioration of cardiovascular disorders in diabetes.

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INVOLVEMENT OF GALECTIN-3 IN CADMIUM INDUCED CARDIAC TOXICITY

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Accumulation of the wide spread environmental toxin cadmium (Cd) in tissues results in toxicity. Heart is one of the most effected tissues. Cd exposure induces inflammation in effected tissues. The present study was focused to evaluate involvement of galectin-3 in Cd toxicity and the relationships between galectin-3 and proinflammatory cytokine levels. Male Wistar rats were exposed to Cd at the dose of 15 ppm for 8 weeks. Inflammatory status in hearts was evaluated with measurement of tissue TNF-α and IL-6 levels. Histopathological examination of heart was carried out by light microscopy. Heart tissue caspase-3 level was used to identify apoptosis. Tissue galectin-3 level was evaluated by ELISA. Heart sizes were increased after Cd toxicity. A significant increase in galectin-3 tissue level was seen after Cd toxicity, this was accompanied with a significant increase in the TNF-α and IL-6 level. Histopathological examination under light microscope suggested a combination of ongoing necrosis and apoptosis. Increased caspase-3 levels were measured after Cd toxicity. Chronic Cd administration induces inflammation and apoptosis in rat hearts. Cd causes increased galectin-3 production in heart tissue. The formation of TNF-α due to Cd exposure may likely trigger this mechanism.

THE PERSPECTIVE OF ZINC THERAPEUTIC AGENTS IN CARDIAC DISEASES TREATMENT

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We studied new zinc-organic antihypoxant specific pharmacology activity at intragastric introduction on cardiac ischemia. Three experimental models were used (cardiac infarction, calcium arrhythmia and experimental adrenaline myocarditis). Survival rate, electrocardiography and histology indices were registered. Preliminary introduction of zinc-organic antihypoxant at cardiac infarction decreases mortality rate, diminishes incidence of myocardium infarction and significantly increases survival rate, diminishes the necrosis site square in myocardium and facilitates faster restoration of coronary blood flow in the ischemia zone. Preliminary introduction of zinc-organic antihypoxant at calcium arrhythmia lengthened the latent period and lengthened of the animal life duration. Introduction of zinc-organic antihypoxant at experimental adrenaline myocarditis prevented considerable decrease of the myocardium contractile activity, diminished ECG signs of the right heart overload and facilitated amplitude restoration of peaks R, S, T and caused regression of inflammatory alterations in cardiomyocytes and significantly facilitated boosted restoration of their normal structure. Clinical administration of Zinc-organic antihypoxant at ischemia patients decreased ischemia attack rate and duration, decreased pCO_2, increased PO_2, increased resistance of loading. The obtained preclinical and clinical data allowed to consider the given new Zinc-organic antihypoxant as a promising agent in treatment of cardiac diseases.

BENEFICIAL ROLE OF SELENIUM ON DIABETES-INDUCED ALTERED ADRENERGIC RECEPTOR RESPONSE OF AORTIC SMOOTH MUSCLE OF THE RATS

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Diabetes mellitus is associated with vascular complications and hyperglycemia causes important changes in smooth muscle cells due to increased production of reactive oxygen species (ROS). Although it is known an important role of matrix metalloproteinases (MMPs) in atherosclerosis, little is known about the effect of hyperglycemia on regulation of MMPs in vascular system. The aim of this study was to evaluate the effect of selenium treatment and for comparison, a MMP inhibitor treatment (0.3 mg/kg sodium selenate or 10 mg/kg doxycycline, intragastrically and daily; for 4-week) on mechanical function and biochemical parameters of streptozotocin-induced diabetic rat aortic smooth muscle. The impaired basal mechanical activity as well as contraction and relaxation responses to adrenergic receptor stimulations of endothelium-denuded aorta were observed to be improved significantly in either selenium or doxycycline treated rats. Gelatin zymography and Western-blot data showed that these treatments also prevented diabetes-induced inhibition of MMP-2 activity and its protein loss. Furthermore, these treatments prevented diabetes-induced increased levels of oxidized protein thiols as well as nitrite levels, significantly. Taken together, our data demonstrate that these beneficial effects obtained with selenium or doxycycline treatment in diabetic aortas appear, in part, to be related to inhibition of ROS production, prevention of beta-adrenergic receptor dysfunction, and regulation of MMP-2 in diabetic vascular smoot muscle. Overall, present data provides preliminary evidence for selenium' or doxycycline' potential as therapautic agents for the vascular reactivity alterations in diabetes.