accumulation of collagen, increased levels of connective tissue growth factor, transforming growth factor β1, tumor necrosis factor-alpha, vascular cell adhesion molecule 1, 3-nitrotyrosine and 4-hydroxy-2-nonenal in the aorta.

Conclusions: These findings suggest that chronic IH may lead to aortic damages characterized by oxidative stress and inflammation, and MT may play a pivotal role in the above pathogenesis process.

GW25-e0790

Effects of (P) RR and PLC-beta3 activation on cardiac hypertrophy in hypertensive rats

Yanling Zhang, Laih Ma, Junyan Wu, Bingsiang Wang
Department of Physiology, Institute of Neurobiology, Taishan Medical University, Tai'an, China

Objectives: (Pro) renin receptor (P) RR, a newly identified member of the renin- angiotensin system, is a promising novel drug target because of its crucial involvement in renal and cardiac end-organ damage, but the mechanism of (P) RR on the end-organ damage remains unclear so far. Recently, some findings support the (pro) renin-(P) RR interaction at exceptionally high (pro) renin levels in vitro. However, the conflicting results obtained with human angiotensin (II) (HRA) in vivo used to argue against the idea that this drug truly blocks the (pro) renin-(P) RR interaction in the intact animals. In this study, we investigated the role of cardiac (P) RR activation on the expression of β3-PLC, PKC and ERK1/2 and on cardiac hypertrophy in hypertensive rats with abdominal aortic ligation.

Methods: Seventy-five SD rats were divided into five groups (n=15 each group) as following: sham operated (SO), rats with the aortic ligation (AL), AL rats were given HRA (14ug kg−1 d−1, SC), AL rats given U73122 (40ug kg−1 d−1, SC) and AL rats given HRA + U73122. MAP was recorded using a tail-cuff method. After 4 weeks of treatment, levels of (P) RR, PLC-beta3, PKC and ERK1/2 in the heart were examined by RT-PCR and western blot. The surface area of cardiomyocytes was measured.

Results: The expression levels of (P) RR and PLC-beta3 significantly increased in the left ventricle in hypertensive rats (P<0.01, respectively). The surface area of cardiomyocytes and MAP rose markedly (P<0.01). HRA treatment significantly reduced the expression of (P) RR and U73122 suppressed the level of PLC-beta3. The combined treatment of HRA and U73122 significantly decreased levels of PKC-α and ERK1/2 in the heart (P<0.01). Meanwhile, the surface area of cardiomyocytes and MAP were decreased after the treatment (P<0.01).

Conclusions: This is the first report demonstrating that treatment of HRA and U73122 decreased levels of (P) RR, PLC-beta3, PKC-α and ERK1/2 in the heart. Meanwhile, the treatment reduced the surface area of cardiomyocytes and MAP. These findings indicate that cardiac (P) RR may activate PLC-beta3, PKC and ERK1/2 signals and result in hypertension and cardiac hypertrophy.

Acknowledgement: This study was supported by the National Natural Science Foundation of China (81270336) and Shangping National Science Foundation (ZR2009CM074).

GW25-e0850

Effect of acute high altitude exposure on lung function and relationship between lung function and AMS

Song Pan, Huang Lan
Cardiovascular Department of Xinqiao Hospital, Third Military Medical University, Chongqing, China

Objectives: To investigate the effect of acute high altitude exposure on lung function and the relationship between lung function and AMS.

Methods: We collected the lung function and Lewis Lake data of 73 subjects (age 18 to 26, male) at sea-level and jummachang (after five days Exposure to 3000m, 3900m).

Results: Compared with sea-level, lung function decreased in FVC, MMF, V50, V25, V10, V5 while FEV1, PEF, V75 did not change. The percent of FVC, FEV1, PEF, MMF were significantly lower in AMS group. There were co-localization and co-immunoprecipitation between ETBR and GRK4 in intact mice, it resulted that ETBR-mediated diuresis and natriuresis was impaired compared with wild type. In wild-type transplanted cells, activation of ETBR inhibited Na+-K+-ATPase activity; while in A142V transplanted cells, the inhibitory effect was lost. There are co-localization and co-immunoprecipitation between ETBR and GRK4 in RPT cells. The linkage of ETBR/GRK4 was higher in wild-type cells than in A142V cells. Similar phenomenon was found in the kidney from WKY and SHRs, SHRs had higher ETBR/GRK4 linkage, accompanied with higher ETBR phosphorylation, which might account for the impaired ETBR function in hypertension.

Conclusions: This study provides a mechanism by which GRK4, via regulation of renal ETBR function, participates in the pathogenesis of hypertension.

GW25-e095

Cardiac Electrical Activity Improved by Overexpression of the Sarco/Plasmalemmal Ca2+-ATPase in Rat Myocardial Failure After Myocardial Infarction Evaluated by Microelectrode Arrays Technology

Fan Ping, Guo Yujin, Wang Hongli, Hou Yuemei
The First Affiliated Hospital of Xinjiang Medical University

Objectives: To explore overexpression recombiant adenosine (rA)-mediated sarcolemmal calcium ATPase (SERCA2a) for cardiac rhythmicity and conductivity in rat heart failure after myocardial infarction and its possibly electrophysiological mechanisms.

Methods: 26 adult male SD rats were randomly divided into three groups: sham group (n=10), rA-β-gal group (n=8) and rA-SERCA2a group (n=8). Sham operation consisted of thoracotomy and cardiac exposure but without coronary artery ligation. rA-β-gal group and rA-SERCA2a group were ligated the left anterior descending coronary artery for rat heart failure animal model after myocardial infarction, while transfecting β-gal and SERCA2a gene into heart respectively. We used ultrasound electrocardiogram for evaluating cardiac diastolic and systolic function, ECG monitoring and microelectrode arrays (MEA) technology for myocardium electrical activity in vitro.

Results: rA carrying SERCA2a and β-gal gene were successfully transfected in heart failure rats. rA-SERCA2a group could improve failing heart function, the ventricular end diastolic volume, left ventricular end-systolic volume, left ventricular ejection fraction and fractional shortening. Compared with the sham group, ECG could be found QT interval prolonged (94.75 ± 6.13 ms vs. 91.02 ± 5.94 ms, P < 0.05) and the incidence rate of premature ventricular contractions (PVC) was 71.5% in rA-β-gal group, but in rA-SERCA2a group QT interval shortened and the incidence rate of PVC was 14.3%. No significant difference in the heart rate of rA-SERCA2a group by MEA records. However, compared with the rA-β-gal group, the maximum field potential, the minimum field potential and field potential duration were prolonged (0.64 ± 0.13 ms vs. 0.82 ± 0.13 ms, 1.35 ± 0.12 vs. 1.88 ± 0.57 ms, 113.23 ± 12.02 ms vs. 124.17 ± 21.08 ms, respectively, n=6, P < 0.05) in rA-SERCA2a group. The field potential duration were statistically different between the infarct zone and the contralateral normal zone (60.36 ± 2.08 ms vs. 103.24 ± 7.35 ms, n=5, P < 0.05) in rA-β-gal group, and field potential duration dispersion in infarct zone with 60 channels record was larger than rA-SERCA2a group. The conduction time was simultaneous in rA-SERCA2a group, and the cardiac electro-conduction activity could keep consistency and improve in myocardial infarction tissue.

Conclusions: Overexpression of SERCA2a may significantly improve left ventricular systolic and diastolic function, as well as it may be reduced incidence of arrhythmias by heart model after myocardial infarction and improve uniform conduction of cardiac electrical activity. MEA technology is an ideal technology for observing rhythm, frequency and conduction activities in cardiovascular disease animal models.

GW25-e1111

Anti-inflammatory Effects of Tanshineone IIA on Oxidative-injured Vascular Endothelial Cells are Mediated by Estrogen Receptor Activation and Through ERK Signaling Pathway

Xin Liu1, Zhenyun Guo1, Xiaojuan Ma1, Ying Zhang2, Mingyang Sun1, Yuting Pan1, Huijun Yin1
1Academy of Chinese Medical Science, 2Center of Cardiovascular Diseases, Xiyuan Hospital, 3Gansu University of Traditional Chinese Medicine

Objectives: To investigate the estrogen protective effect and mechanism of Tan- shineone IIA on oxidative-injured vascular endothelial cells.
Methods: We established low-estrogen atherosclerotic animal model by feeding oestradiol and high-fat diet, and oxidative-injured cells model were induced by ox-LDL in HUVECs. Tanshinone IIA (mice: 30mg/kg, 60mg/kg, cells: 0.1μM, 1μM, 10μM) was given to the mice and cells, and estrogen (mice: 0.13mg/kg/ d; cells: 0.01μM) and estrogen receptor antagonist (ICI182780) mix, mice: 65μg/kg; cells: 0.1μM) were also designed to be given. The levels of NF-ΚB, ICAM-1, AP-1, E- selectin and 17β Estradiol (E2) in serum and the levels of NF-ΚB, ICAM-1, AP-1 and E-selectin in supernatant were measured by ELISA. The expression of P-ERK1/2 in mice aorta and cells and inhibited the expression of ER

Conclusions: was similar to the estradiol, and could be inhibited by ICI182780.

Alterations of the calreticulin-STAT3 pathway associates with mitochondria damage in selenium deficient rat hearts

Ming Zhang1, Yanye Zhu1, Rui Wang2, Yali Li1, Jie Zhang1, Qihong Zhang1, Jin Wei1
1Department of Respiratory Medicine, the Second Affiliated Hospital, Xi’an Jiaotong University, Xi’an China, 2Department of Cardiology, the Second Affiliated Hospital, Xi’an Jiaotong University, Xi’an China

Objectives: To study the changes of calreticulin-STAT3 signaling pathway and its effect on cardiac mitochondria damage in selenium deficiency rat hearts.

Methods: Twenty male Sprague-Dawley rats were randomized into normal control group (n=8) and selenium deficiency model group (n=12). When rats were fed for 20 weeks, the cardiac function was measured by hemodynamic studies. The signal molecules involved in the calreticulin-STAT3 pathway were investigated using real-time PCR and western-blot. The mitochondrial structure and function were assessed.

Results: Compared with the control group, the rats in the model group had reduced systolic and diastolic function. Cardiac mRNA expression was 4.6-fold higher in the model group than that in the control group, and the protein level of calreticulin was 3.3-fold higher than that in the control group (P<0.05). The protein expression of STAT3 and P-STAT3 in the whole myocardium and cardiac mitochondria were both significantly down-regulated in the model group (P<0.05). The mRNA and protein levels of manganese superoxide dismutase (MnSOD), downstream to STAT3, were also significantly decreased in the model group (P<0.05). Under electron microscopic observation, the cardiac mitochondria in the model group were swelling with fractured or dissolved cristae. The mitochondrial membrane potential level of the isolated fresh myocardium decreased, and the enzyme activities of succinate dehydrogenase and cytochrome c oxidase in the model group were all significantly decreased as compared with the control group (P<0.05).

Conclusions: The development of selenium deficiency induced cardiomyopathy in rats, might be due to the up-regulated expression of calreticulin, which inhibits STAT3 phosphorylation in both the whole cell and mitochondrial fraction.

Curcumin reduces cardiac fibrosis in rats and 20 mmol) for 1 h before treated with Ang II.

Conclusions: LOX-1 plays a critical role in ox-LDL-induced endothelial cell apoptosis via the ER stress pathway.

Establishment and evaluation of reparative myocardial fibrosis model in rat

Lv Shichao1, Wu Meifang2, Li Meng3, Wang Qiang3, Xu Ling2, Wang Xiaoqiang2, Jing Zhai2
1The First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, 2Tianjin University of Traditional Chinese Medicine

Objectives: Establish the reparative myocardial fibrosis rat model and evaluate it.

Methods: Mix the pig cardiac myosin (the concentration is 6.4 mg/ml) with equal volume proportion of complete Freund’s adjuvant (CFA) (with 1mg mycobacterium tuberculosis per milliliter by thermal inactivation), then push them in 4°C refrigerator repeatedly to achieve the aim of sufficient emulsification, form a kind of emulsion which is sticky and water-in-oil (the final concentration of the pig cardiac myosin is 3.2mg/ml). Each Lewis rat was immunized with 1mg/0.3ml of an emulsion containing cardiac myosin with an equal volume of CFA by subcutaneous injection on days 0 and 7. Both the left and right hind leg foot pad of the rat was injected. Negative control rat were immunized with PBS/CFA. On days 28 after the first injection, take the material and weigh the body weight, the quality of heart and left ventricle. Hematoxylin-eosin (HE) staining and Masson staining was performed on paraffin-embedded heart sections. The sample alkali hydrolysis method was used to detect myocardial tissue hydroxyproline (HYP) content. Enzyme linked immunosorbent assay (ELISA) was conduct to detect the level of Carboxyterminal propeptide of procollagen type I (PICP), N-terminal peptide of procollagen type III (PIIINT) and type I collagen (CTX-I) in serum.

Results: Compared with negative control rats, cardiac index and left ventricular mass index increased significantly in model rats. Myocardium of HE staining showed increased inflammatory cell infiltrate and cardiac myocyte hypertrophy with myocardium decreased and necrosis in model rats. That of Masson staining showed the reparative myocardial fibrosis transformation that large bundled quantity of blue myofibril, deposited and disordered arrangement of collagen in myocardial matrix and fibre replaced necrotic myocardium. Content of HYP in myocardium of model rats increased significantly compared with negative control rats. There was a higher level of PICP and PIIINT indicating collagen synthesis and CTX-I indicating collagen degradation in model rats serum than negative control rats.

Conclusions: Pig cardiac myosin could induce the typical reparative myocardial fibrosis in Lewis rat.

Curcumin inhibits cardiac fibrosis in vitro and in vivo by inhibiting myofibroblast differentiation

Ma Jin, Shiyu Ma, Chunhua Ding
Guangdong Provincial Hospital of Chinese Medicine

Objectives: Cardiac fibrosis is a hallmark of heart disease and plays a vital role in cardiac remodeling during most types of cardiac injury. Curcumin has been demonstrated to exhibit a variety of potent beneficial effects such as antioxidant, anti-inflammatory and cardioprotective potential. However, the effect of curcumin on fibrosis in cardiac fibrosis has not yet been investigated.

Methods: Isporetofen (ISO) -induced cardiac fibrosis rats were treated with curcumin (150 or 300 mg/kg/d) for 28d. In addition, cardiac fibroblasts were treated with Ang II for 24 h alone or pretreated with curcumin in different concentrations (5, 10, and 20 μmol/L) for 1 h before treated with Ang II.

Results: Curcumin significantly reduced cardiac fibrosis in rats by decreasing interstitial and perivascular myocardial collagen deposition and cardiac weight index (2.695±0.025 in control vs. 3.144±0.038 in ISO group, 3.165±0.031 in ISO+Cur-L group, P<0.05 vs. ISO group alone; 2.956±0.026 in ISO+Cur-H group, P<0.05 vs. ISO group alone) as well as reducing protein expression of collagen I (1.376±0.169 in ISO+Cur-H group, P<0.05 vs. 2.624±0.215 in ISO group) and III (0.831±0.096 in ISO+Cur-H group, P<0.05 vs. 1.214±0.158 in ISO group) in hearts. Curcumin directly inhibited angiostatin II (Ang II) -induced fibroblast proliferation and collagen type I/III expression in cardiac fibroblasts. We also found that curcumin inhibited fibrosis by inhibiting myofibroblast differentiation. Curcumin also decreased transforming growth factor (TGFI-β), matrix metalloproteinase (MMP) -9 and tissue inhibitor of metalloproteinase (TIMP)-1 expression but had no effects on Smads in Ang II incubated cardiac fibroblasts.

Conclusions: Curcumin reduces cardiac fibrosis in rats and Ang II-induced fibroblast proliferation, by inhibiting myofibroblast differentiation and decreasing collagen synthesis and accelerating collagen degradation via regulation of TGF-β1, MMPs, TIMPs. The present findings provided novel insights and underscore the therapeutic potential of curcumin as an anti-fibrotic agent for the treatment of cardiac fibrosis.

CKIP-1 can regulate physiological cardiac hypertrophy through inhibition of HDAC4 phosphorylation

Ling Shukuan, Zhang Pengfei, Li Yuheng, Zhao Dingsheng, Sun Weijia, Xu Zi, Zhong Guohui, Li Qi, Song Jinpeng, Li Yinghai, Li Yingxian
State Key Laboratory of Space Medicine Fundamentals and Application, China Astronaut Research and Training Center, Beijing, China