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Effect of sarcolipin silencing in attenuating ventricular arrhythmias in diabetic cardiomyopathy

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OBJECTIVES Our previous investigation showed that the expression of sarcolipin was elevated in heart of rats with experimental diabetic cardiomyopathy. It was believed that the intracellular calcium homeostasis was related with sarcolipin which regulates SERCA. This study was aimed to investigate the effects of sarcolipin silencing on ventricular arrhythmia in diabetic cardiomyopathy.

METHODS Animal model of diabetic cardiomyopathy was established. Adenoviral vector carrying specific siRNA against sln was administrated to animals. The knock-down effect of the siRNA was testified by western blotting and real- time PCR. The ventricular arrhythmias were monitored by ECG.

RESULTS The adenoviral vector administration significantly down-regulated expression level of sarcolipin in cardiac tissue from animal model of diabetic cardiomyopathy. The incidence of ventricular arrhythmias decreased significantly after sarcolipin silencing.

CONCLUSIONS Silencing of sarcolipin could inhibit ventricular arrhythmias in diabetic cardiomyopathy.

GW27-e1134

Effects of different intensity treadmill running on myocardial mitochondrial substrates utilization characteristics in rats

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OBJECTIVES To investigate the influence of different intensity of treadmill exercise on mitochondrial respiration function, mitochondrial oxidation capability of different substrates originated from carbohydrate and fatty acid respectively and the underlying molecular mechanism.

METHODS Male Sprague-Dawley rats were randomly divided into 3 groups, the sedentary control group(C, n=7), moderate intensity treadmill running group (78%VO2max) (ME, n=6) and low intensity treadmill running group (68%VO2max) (LE, n=6). The treadmill running regimes of LE and ME groups were established according to Bedford[1] as below, (1) LE group: 5? grade, 15m.min-1, 64%VO2 max, time duration 30 minutes, (2) ME group: 10?, 15m.min-1, 75% VO2 max, time duration 30 minutes. The training cycle lasted for 8 weeks, 5 days per week. After establishing the model, rats of 3 groups were anesthetized by peritoneal injection of sodium pentobarbital (45mg.kg-1). Immediately after anesthesia, the left ventricular tissue was isolated for mitochondrial function measure. The mitochondrial respiratory function of permealized myocardium was detected in situ by the High-resolution Respirometry. The Palmitoyl carnitine+Malate (Pal+Mal) and Octanoyl carnitine+Malate (Oct+Mal) were respectively titrated to test the activity of electron transferring flavoprotein (ETF). The Pyruvate (Pyu), Glutamate (Glu), and Succinate (Suc) were added as glucose originated substrates to test the mitochondrial electron transfer chain (ETC), Complex I and II. Finally, the PPARα and Akt2 gene and protein levels were measured by RT-PCR and Western Blot respectively.

RESULTS (1) When Pal+Mal or Oct+Mal were titrated as substrates, compared to the C group, the respiration rates of LE and ME groups were increased insignificantly ($P > 0.05$), and compared to the LE group, the ME group was increased insignificantly ($P > 0.05$). (2) When Pyu or Glu were titrated, compared to the C group, the respiration rate of the ME group were increased significantly ($P < 0.05$). (3) When Suc was titrated as substrates, compared with the C group, the respiration rate of the ME group was increased significantly ($P < 0.05$). (4) Compared to the C group, the PPARα mRNA and Akt2 mRNA of ME and LE groups were increased insignificantly ($P > 0.05$). Compared to the LE group, the PPARα mRNA of ME group was increased insignificantly ($P > 0.05$), and the Akt2 mRNA expression was increased significantly ($P < 0.01$). (5) Compared to the C group, the PPARα and Akt2 protein levels of LE and ME groups were increased significantly ($P < 0.01$). Compared to the LE group, the PPARα protein in the ME group was increased insignificantly ($P > 0.05$) and the Akt2 protein level was increased significantly ($P < 0.01$).

CONCLUSIONS A greater reliance on fat resourced energy substrates occurred during low intensity treadmill running (68%VO2max) and a greater reliance on carbohydrate as energy substrate resource occurred during high intensity exercise (78%VO2max) in rat heart myocardial energy metabolism.

GW27-e1145

Chronic intracerebroventricular infusion of metformin inhibits salt-sensitive hypertension in rats via attenuation of oxidative stress in the hypothalamic paraventricular nucleus

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OBJECTIVES This study was designed to determine whether metformin, an antidiabetic agent, exerts antihypertensive effects in rats with salt-sensitive hypertension through attenuation of oxidative stress in the hypothalamic paraventricular nucleus (PVN).

METHODS Dahl salt-sensitive rats received a high-salt (HS, 8% NaCl) diet or a normal-salt (NS, 0.3% NaCl) diet and were treated with intracerebroventricular (ICV) infusion of metformin or vehicle for 6 weeks. The rats were divided into 4 groups: the normal-salt diet control group [0.3% NaCl+intracerebroventricular (ICV) artificial cerebrospinal fluid (aCSF)], the normal-salt diet with MET group (0.3% NaCl+ICV MET 25μg/d), the high-salt diet control group [(8% NaCl+ICV aCSF), the high-salt diet with MET group [8% NaCl+ICV MET 25μg/d]. Mean arterial pressure (MAP) and heart rate (HR) were measured every week by a tail-cuff occlusion. Reactive oxygen species (ROS), subunits of NAD(P)H oxidase, superoxide dismutase (SOD), the ennin-angiotensin system (RAS) components, inflammatory cytokines (ICs), neurotransmitters levels in the PVN were determined by immunofluorescence, immunohistochemistry, western blot, high-performance liquid chromatography (HPLC). Norepinephrine (NE, an indicator of sympathetic activity) levels in plasma were examined by enzyme-linked immunosorbent assay (ELISA).

RESULTS High-salt rats had significantly increased MAP, plasma norepinephrine compared with normal-salt rats ($P<0.05$). ICV infusion of metformin decreased MAP, plasma norepinephrine in high-salt rats ($P<0.05$). In addition, high-salt rats showed higher levels of NOX-2, NOX-4, ROS, angiotensin-converting enzyme (ACE), angiotensin II type 1 receptor (AT1-R), IL-1β, IL-6, glutamate, NE and tyrosine hydroxylase (TH) and lower levels of SOD, IL-10, γ-aminobutyric acid (GABA) and the 67-kDa isoform of glutamate decarboxylase (GAD67) in the PVN compared with normal-salt rats ($P<0.05$). These above biochemical changes associated with salt-sensitive hypertension were significantly prevented by ICV infusion of metformin in high-salt rats ($P<0.05$).

CONCLUSIONS Our findings suggest that ICV infusion of metformin significantly decreases the sympathetic activity and blood pressure in salt-induced hypertension by attenuating oxidative stress, suppressing the activation of RAS and restoring the balance of inflammatory cytokines and neurotransmitters in the PVN.

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Angiotensin 1-7 Protects against Ox-LDL -Induced Endothelial Endoplasmic Reticulum Stress and Apoptosis

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OBJECTIVES To investigate the protective effect of Ang 1-7 against ox-LDL -induced endoplasmic reticulum stress(ERS) and apoptosis via Mas Receptor in Human umbilical vein endothelial cells(HUVECs),and provide a potential therapeutic strategy that the Ang 1-7/Mas receptor axis to treat ox-LDL-induced cardiovascular diseases related to ER stress.

METHODS HUVECs were cultured in 1640 medium containing 12% fetal bovine serum,1% penicillin and streptomycin. After 50% confluence was obtained, they were treated medium without FBS for 12 h, and later were replaced with new complete media, Experiment was divided into five groups: the control group; the ox-LDL group:cells were exposed to ox-LDL (75mg/L) 30 min; the Ang-(1-7)+ ox-LDL group: cells