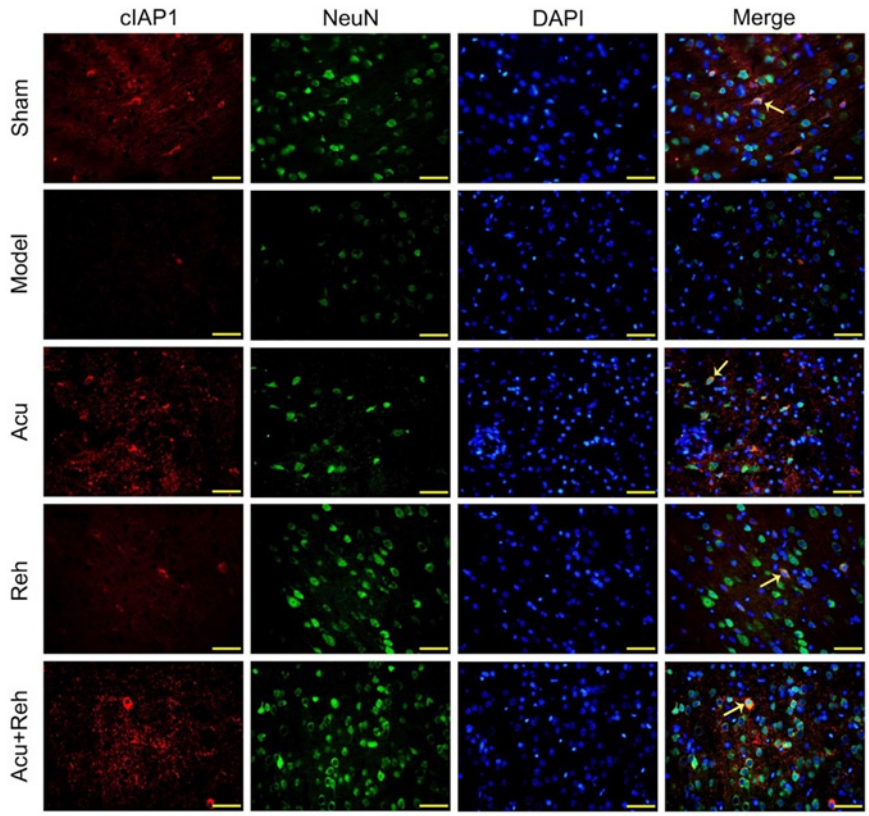

Fig 1 Immunofluorescence double labeling of cIAP1 and NeuN

Note: cIAP1(Red), NeuN(Green), DAPI(blue). The yellow arrows refer to co-localization cells of cIAP1 and NeuN.

EFFECT OF QIANGXIN CAPSULE ON ENDOPLASMIC RETICULUM STRESS RELATED PERK-EIF2A PATHWAY IN RATS WITH ADRIAMYCIN-INDUCED CHRONIC HEART FAILURE

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OBJECTIVE: To investigate the effect of Qiangxin capsule(QXC) on changes of cardiac structure and function and its putative mechanism by investigating myocardial pathological and apoptosis station, and PERK-eIF2α protein expression in rats with chronic heart failure.

METHOD: The chronic heart failure(CHF) model in rats was administrated by intravenous injected adriamycin hydrochloride 3mg/kg in 1,3,5week and 1mg/kg in 2,4,6 week, once a week, for 6 times. The control group was intravenous injected by 0.9% Nacl, once a week, for 6 times. Six weeks after the procedure, rats were randomly classified into 5 groups: model group, Enalapril(1.8mg/kg),low QXC dose(0.66g/kg),medium QXC dose(1.32g/kg), and high QXC dose(2.64g/kg).The administration of drugs was given from the 7th week after modeling, and the treatments continued for 4 consecutive weeks. After the treatment, we observed the general state included diet, stool, hair color, urine, respiration, et al. of each groups and measured the heart weight index. Changes of cardiac function were evaluated by echocardiography. Myocardial morphology were investigated by hematoxylin and eosin staining. The myocardial apoptosis was detected by TUNEL. The related protein expression of myocardial PERK-eIF2α pathway were detected by western blotting.

RESULTS:

1.Qiangxin Capsule Attenuates Heart Function Injury in CHF rats:Compared with the control group, The LVEDD and LVESD of model group were significantly increased(P<0.01),and the LVEF and LVFS were significantly decreased(P<0.01).Compared with the model group, the LVEDD and LVESD in each treatment group was significantly decreased(P<0.01), Meanwhile the LVEF and LVFS were significantly increased(P<0.01).Com-

pared with the Enalapril group, the LVEDD and LVESD of the low dose group were significantly increased(P<0.01) and the LVEF and LVFS were decreased (P<0.05,P<0.01),the LVEDD and LVESD of middle dose group and high dose group were increased no statistical significance(P>0.05),the LVEF and LVFS were decreased no statistical significance(P>0.05).The LVEF and LVFS of high dose group was higher than the low dose group(P<0.05).

2.Qiangxin Capsule Alleviates the Heart Tissue Histologic:The microphotographs showed that in sham group myocardial fibers were arranged orderly, cytoplasmic staining was uniform, and nucleus boundaries were clear.It was observed that in CHF group the range of myocardial cells in heart tissue was in disorder and there is marked neutrophilic infiltration around the myocardial cells. Myocardiocyte disarrangement and fibrosis accretion were observed in CHF group as well.In rats group with 4 weeks of treatment with Enalapril or Qiangxin Capsule, myocardiocyte disarrangement, neutrophilic infiltration and fibrosis accretion were alleviated compared to rats with Adriamycin.

3.Qiangxin Capsule Attenuates Myocardial Apoptosis in CHF Rats:Compared with the control group, the apoptosis index of the model group was significantly increased (P<0.01). Compared with the model group, the apoptosis index of myocardial cells in each treatment group was decreased, the Enalapril group and middle dose group were significantly decreased(P<0.01). Compared with the western medicine group, the apoptosis index in the low dose group and middle dose group were significantly increased(P<0.01),high dose group were increased no statistical significance(P>0.05).The apoptosis index of high dose group was lower than the low dose group(P<0.05).

4. PERK-eIF2α pathway in the Heart of chronic heart failure Rats Was Inhibited by Qiangxin Capsule:Compared with the control group, the expression of pERK, p-PERK, eIF2α, p-eIF2α,and ATF4 in model group were significantly increased (P<0.01). Compared with the model group, the expression of PERK, p-PERK, eIF2α, p-eIF2α and ATF4 in each treatment group were decreased differently (P<0.05, P<0.01). Compared with the Enalapril group , the low dose group was increased (P<0.05),middle dose group and high dose group were increased no statistical significance(P>0.05)..The PERK、p-PERK、p-eIF2α、ATF4 of high dose group was lower than the low dose group(P<0.05).

CONCLUSION:

1.Qiangxin Capsule could improve the index of echocardiography in CHF rats, reduce LVEDD and LVESD, increase LVEF and LVFS, improve the heart function of CHF rats.

2.Qiangxin Capsule could improve myocardial structure of CHF rats.

3.Qiangxin Capsule could reduce the cardiac muscle cell apoptosis index in CHF rats.

4.Qiangxin Capsule could reduce the GRP78 protein expression and inhibit the related protein expression of PERK-eIF2α pathway. It also could reduce the accumulation of misfolded proteins, decrease the apoptosis of myocardial cells and delay ventricular remodeling.

Keywords: Chronic Heart Failure; Apoptosis; PERK-eIF2α pathway; Endoplasmic Reticulum Stress; Qiangxin Capsule

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ELECTRON-MICROSCOPIC LOCALIZATION OF ADENYLATE CYCLASE IN THE RAT TRACHEAL EPITHELIUM DURING COLD EXPOSURE

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Abstract: In this study, a reaction was performed showing the localization and activity of adenylate cyclase in the mucosa of the trachea in normal and prolonged cold exposure to the body. The obtained data on the localization and activity of adenylate cyclase suggest that in intact rats in the mucosa the greatest activity of adenylate cyclase is detected on the surface of the cilia of the single-layered ciliated epithelium and on the surface of the endothelium of the blood capillaries of the submucosa of the trachea. As for the activity of adenylate cyclase in the experiment, a prolonged cold exposure results in a decrease in the intensity of its work.

Key words: Epithelium of rat trachea, adenylate cyclase, cold action.

Material and methods: The study was carried out on 20 white pedigreed adult male rats with a body weight of 150-200 g. In the study, the animals were divided into 2 groups: the first - control consisted of 10 animals, which were kept in the vivarium during the whole experiment at T = 22 ° C. The second group, consisting of 10 animals, was exposed to a daily 3-hour total cold exposure for 28 days at T minus 15 ° C. The object of our study was the caudal sections of the mucous membrane of Trachea rats. Tissue samples taken were used for the production of semi-thin and ultra-thin sections. To do this, from the caudal part of the trachea, pieces of tissue 1 × 1 mm were cut out. To study the localization and activity of adenylate cyclase, the method of electronic histochemistry according to Raik et al., (Gaier, G., 1974) was used. The investigation of ultrathin sections was carried out on an electron microscope of the translucent type “Technai G2 Spirit Twin” - Holland.

Results and discussion: In this study, a reaction was performed showing the localization and activity of adenylate cyclase in the mucosa of the trachea in normal and prolonged cold exposure to the body. AC is a transmembrane protein, part