

[gw22-e0567]

SYMPATHETIC STORM AGGRAVATE ABNORMAL KV4.2 ION CHANNEL MEMBRANE TRANSPOSITION IN RAT CARDIOMYOCYTES THROUGH ENDOPLASMIC RETICULUM STRESS

Zhuo Xiaozhen, Gong Min, Wang Xuehui, Zhang Yong, Zhang Ting, Wu Yue, Wang Tingzhong, Ma Aiqun *Cardiovascular Department, First Affiliated Hospital, Xi'an Jiaotong University, Xi'an, China*

10.1136/heartjnl-2011-300867.54

Objectives The excessive activation of sympathetic nerve can lead to heart failure which causes heart remodeling, including both electrical and structural remodelling. Whether the endoplasmic reticulum (ER) stress mechanism on the electrical remodelling of heart failure induced by sympathetic storm is still poorly understood. This study investigated whether excessive activation of sympathetic nerve causes aberrant ER stress and electrical remodelling in heart failure.

Methods Heart failure was induced in SD rats by different dose of isoproterenol (ISO) (85 mg/kg and 170 mg/kg) with the same amount of physiological saline as control. At the end of two weeks, hemodynamic and plasma BNP was performed and measured to evaluate the heart function. Real-time quantitative PCR and western blot were used to detect the expression of ER stress associated elements and Kv4.2 both at the mRNA level and the protein level. Moreover, the primary cultured neonatal rat ventricular myocytes after quiescence for 24 h were exposed to different concentration of ISO (0, 10, 20 and 100 $\mu\text{mol/l}$). Immunofluorescence, Real-time quantitative PCR and western blot were also used to investigate the of ER stress and the location of Kv4.2 on cell membrane of neonatal rat ventricular myocytes.

Results The hemodynamic examination findings showed significant ISO-induced heart dysfunction groups compared with the control group ($p < 0.05$), but there were no significant changes in the two ISO-dose-induced groups. Compared with the control group, with the increase of the ISO-dose-induced groups, the mRNA expression of ATF6 and GRP78 have significantly increased ($p < 0.05$). However, the protein expression of Kv4.2 on the cell membrane of rat ventricular cardiomyocytes have significantly decreased ($p < 0.05$). The intensity of ER stress in ISO-exposed neonatal rat ventricular myocytes aggravated in a dose-response dependence manner, as evidenced by mRNA expressions of ATF6, XBP-1 and GRP78 significantly increased ($p < 0.05$), and the protein expression of ATF6, XBP-1, GRP78 and p-eIF2 α significantly increased ($p < 0.05$), with the ATF6 translocation and transactivation into the nucleus of the cardiomyocytes. Meanwhile, the membrane Kv4.2 protein expression significantly decreased in the ISO dose of 20 $\mu\text{mol/l}$ (deceased by $39 \pm 9\%$, $p = 0.012$) and the ISO dose of 100 $\mu\text{mol/l}$ (deceased by $51 \pm 11\%$, $p = 0.003$) compared with the control group, however, there are no change to total protein expression of Kv4.2.

Conclusion The excessive activation of sympathetic nerve can lead to the abnormal membrane translocation of Kv4.2 and ventricular electrical remodelling through the aberrant endoplasmic reticulum stress, which could be helpful to understand the electrical remodelling in sympathetic storm related heart failure.