BASIC AND TRANSLATIONAL MEDICINE

BASIC RESEARCH OF CARDIOVASCULAR DISEASE

GW28-e0027

Chronic Neuropathic Pain Sensitizes Heart to Ischemic Injury: Role of Carbonyl Stress

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OBJECTIVES Pain is not a symptom that exists alone, but whether chronic pain enhances susceptibility to myocardial ischemia/reperfusion (MI/R) injury and the underlying mechanisms remain unknown. Reactive aldehydes contribute to pain pathologies and cardiac injury, suggesting that aldehyde dehydrogenase (ALDH2), which detoxifies aldehydes, may regulate chronic pain related MI/R injury. The aim of this study was to investigate the roles of ALDH2 in chronic pain related MI/R injury and to elucidate the underlying mechanisms.

METHODS In this study, chronic neuropathic pain was induced by chronic compression of the dorsal root ganglion (CCD). CCD for 2 weeks, ALDH2 KO or wild-type (WT) littermates were subjected to in vivo MI/R.

RESULTS CCD-WT mice exhibited heightened nociception and correlated with circulating aldehyde (4-HNE) accumulation and cardiac protein carbonylation. CCD induced 4-HNE overload provoked cardiac SIRT1 carbonylative inactivation and impairment the cardioprotection of LKB1-mediated AMPK activation, which resulting in enhanced MI/R injury and higher mortality compare with pain free WT mice. Chronic neuropathic pain enhanced susceptibility to MI/R injury was further exacerbated by ALDH2 deficiency in which associated with more impaired SIRT1-LKB1-AMPK signaling. However, treatment of CCD-WT mice with ALDH2-selective activator (Alda-1) or cardiac specific ALDH2 upregulation by AAV9-cTNT-mediated gene delivery significantly reduced chronic neuropathic pain-induced SIRT1 carbonylative inactivation and decreased MI/R injury (minor infarct size, less apoptosis, and elevated cardiac function).

CONCLUSIONS These results strongly suggest that elevated reactive aldehyde concentration, like that observed in the presence of chronic pain, may render cardiomyocytes more susceptible to MI/R injury by SIRT1 carbonylative inactivation and impairment the cardioprotection of LKB1-mediated AMPK activation. ALDH2 activation blocked reactive aldehyde overproduction induced carbonyl stress and attenuated myocardial ischemic vulnerability in chronic pain individual.

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Relationship Between Ventricular Tachycardia Occurrence and Sympathetic Innervation and Myocardial Perfusion Disorders in Patients With the Coronary Artery Disease and Implantable Cardioverter Defibrillator

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OBJECTIVES Identify the relation between ventricular tachycardia occurrence and sympathetic innervation and myocardial perfusion disorders in patients with coronary artery diseases and ICD and identify potential predictors of ventricular tachycardia in these patients.

METHODS Sixteen patients aged 48 to 82 years, mean age 64,4 ± 8,3 years, with coronary artery disease and myocardial infarction, I-III functional class (FC) of angina pectoris and I-III FC of chronic heart failure (CHF) by NYHA classification were included to research. Ejection fraction (EF) of the left ventricle was 46,1 ± 12,1%. All patients with ICD implantation indications before the manipulation underwent single-photon emission computed tomography (SPECT) with thallium-199 (perfusion defects detecting) and iodine-123-meta-iodobenzylguanidine (123I-MIBG) (cardiac sympathetic innervation assessment). After ICD implantation, all patients received an appropriate antiarrhythmic therapy. The following parameters were assessed after 3 months: the incidence of ventricular tachycardia (VT), FC of angina pectoris, FC of CHF and left ventricular EF. Patients were divided into two groups by the presence of VT episodes. The first group included 12 (75%) patients with registered VT. The second group consisted of 4 (25%) patients without VT.

RESULTS The first group consisted of 2 patients with I FC of angina pectoris, II - 6 patients, III - 4 patients. II FC of CHF diagnosed in 11 patients, III - 1 patient. The second group consisted of 1 patient with I FC of angina pectoris, II - 2 patients, III - 1 patient. I FC of CHF diagnosed in 1 patient, II - 2 patients, III - 1 patient. In first group left ventricle perfusion defect was 26,7 ± 12,7%, in second group - 7,7±5,2% ($p<0,0002$). In first group defect of 123I-MIBG accumulation was 40,0 ± 14,5%, in second group - 8,5±7,2% ($p<0,0001$). Left ventricular EF in the first group was 42,0 ± 9,6%, in second group - 58,5±12,7% ($p<0,001$). Preliminary results showed that II and III FC of angina pectoris and CHF, left ventricle EF decrease less than 42%, myocardial perfusion defect more than 26.7% and MIBG defect accumulating more than 40.0% in first group patients, are potential predictors of VT comparing with second group.

CONCLUSIONS These preliminary results showed that disorders of the sympathetic innervation and myocardial perfusion estimated by SPECT with 123I-MIBG and thallium-199, as well as the FC of angina pectoris and CHF and left ventricular systolic function decrease, influence on the incidence of VT in patients with coronary artery disease and implanted ICD.

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Activation of Angiotensin II Type 1 Receptor Increases D4 Dopamine Receptor Expression in Rat Renal Proximal Tubule Cells

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OBJECTIVES Both dopaminergic and renin-angiotensin systems play important roles in regulation of blood pressure. Our previous study showed that stimulation of dopaminergic D4 receptor reduced angiotensin II type 1 (AT1) receptor expression in renal proximal tubule (RPT) cells. In the present study, we test if AT1 receptor in return regulates D4 receptor expression and function in RPT cells.

METHODS Expression of D4 receptor from Wistar-Kyoto (WKY) or spontaneously hypertensive rats (SHRs) RPT cells and renal cortex tissues were determined by western blot, and Na+-K+ ATPase activity was determined by using enzyme assay. Urine volume and urine sodium of WKY rats and SHRs treated with or without D4 receptor stimulator were collected.

RESULTS As a result, activation of AT1 receptor with angiotensin II (Ang II) increased D4 receptor protein expression in RPT cells, which was blocked by calcium influx blocker nicardipine. D4 receptor agonist PD168077 inhibited Na+-K+ ATPase activity in WKY RPT cells but not SHR RPT cells. Ang II pretreatment promoted D4 receptor-mediated inhibition of Na+-K+ ATPase in RPT cells from WKY rats but not SHRs. Meanwhile, Ang II pretreatment augmented the natriuretic effect of PD168077 in WKY rats but not in SHRs.

CONCLUSIONS In conclusion, AT1 stimulation can regulate the expression and natriuretic function of dopaminergic D4 receptor in RPT, which might be involved in the pathogenesis of essential hypertension.

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Roles of Cardiac (P)RR And PLC-β3 in Hypertensive Rats With Aortic Constriction

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OBJECTIVES The renin-angiotensin system (RAS) plays an important role in cardiac remodeling. Ang II induces cardiac hypertrophy and fibrosis in hypertension. Recently, some findings support the (pro) renin-(Pro)renin receptor (P)RR interaction at exceptionally high (pro) renin levels in vitro. However, the precise mechanisms of the (P)RR signaling in the heart remain obscure. The aim of this study was to investigate the roles of cardiac (P)RR and its downward signals on mean arterial pressure (MAP) in rats with abdominal aortic