DIFFERENTIAL EFFECTS OF GLP-1 RECEPTOR AGONIST APPLICATIONS ON THE REMODELING OF AGING-HEART

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Glucagon-like peptide-1 receptor (GLP-1R) agonists improve cardiovascular dysfunction via the pleiotropic effects behind their receptor action. However, it is unknown whether they have cardioprotective action in aging-heart. Therefore, we examined the effects of GLP-1R agonist liraglutide treatment (4 weeks) on systemic parameters of aged rats (24-mo-old) compared to those of adult rats (6-mo-old) such as electrocardiograms (ECGs) and blood pressures. At cellular levels, action potential (AP) parameters, ionic currents, and Ca^{2+}-regulation were examined in freshly isolated ventricular cardiomyocytes. The liraglutide treatment of aged rats significantly reserved the prolongations in ECG parameters and increases in both systolic and diastolic pressures together with recoveries in plasma oxidant and antioxidant status. The prolonged AP durations and depolarized membrane potentials of the isolated cardiomyocytes from the aged rats were found to be normalized via recoveries in K^+-channel currents with liraglutide treatment. The alterations in Ca^{2+}-regulation including leaky-ryanodine receptors could be also reserved via recoveries in Na^+/Ca^{2+}-exchanger currents with this treatment. Direct treatment of isolated aged-rat cardiomyocytes with liraglutide could recover the depolarized mitochondrial membrane potential, the increase in both reactive oxygen and nitrogen species (ROS and RNS), and cytosolic Na^+-level, although Na^+-channel currents were not affected by aging. Interestingly, the liraglutide treatment of aged-rat cardiomyocytes provided significant inhibition of activated SGLT2 and recoveries in the depressed insulin receptor substrate 1 (IRS1) and increased protein kinase G (PKG). The recovery in the ratio of phospho-endothelial nitric oxide (eNOS) level to eNOS protein level in the treated ventricular cardiomyocytes implies the involvement of liraglutide-associated inhibition of oxidative stress-induced injury via IRS1-eNOS-PKG pathway in aging-heart. Interestingly, marked irregular atypical fibrillations and significant prolongation of the QT intervals in in situ ECGs were observed following an acute GLP agonist application. Unlikely to adult group, GLP agonism prolonged APs, reduce K-currents and increased the Ca^{+2}-spark frequency in the aged cardiomyocytes, while Na-channels become resurgent after GLP activation implying higher propensity for arrhythmias. Overall, our data, for the first time, provide important information on the direct cardioprotective effects of GLP-1R agonism in the hearts of aged rats in a differential manner as chronic or acute effects.