The mechanism underlying the role of CaMKII-mediated phosphorylation of Cav1.2 channel in cardiac hypertrophy and the effects of new-type peptide

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[Background] Cardiovascular disease such as hypertension may induce cardiac hypertrophy and pathological remodeling. Ca2+, as an important intracellular second messenger, is an important initiating factor of hypertrophy-related signaling pathways. Cav1.2 channel is the major route for Ca2+ influx in cardiomyocytes, meanwhile it receives the regulation from Ca2+ itself and a variety of protein kinases. Among the kinases, calmodulin (CaM)-dependent protein kinase II (CaMKII) is a kinase that can be activated at high Ca2+ concentration through the mediation of Ca2+/CaM, forming the activated form of CaMKII, p-CaMKII, through autophosphorylation. Some phosphorylation sites of CaMKII on the C-terminal tail of Cav1.2 have been confirmed, which are S1516/1574 and T1603. In recent years, the development of protein kinase inhibitors in the treatment of cardiac hypertrophy has made some progress, but most stay in vitro effective. In the present study, we designed a new-type peptide named as peptide-1, which can mimic the binding domain of CaMKII and CaM in Cav1.2 channel, and then reduce Cav1.2 channel phosphorylation. [Methods] SD rats were randomly divided into three groups: control group (Control), myocardial hypertrophy group (ISO) and peptide treatment group (peptide). The model of cardiac hypertrophy was prepared by subcutaneous injection of isoproterenol. The peptide group was given intraperitoneal injection of 15mg/kg body weight peptide as giving isoproterenol. [Results] The results showed that the ratio of HM/BM in ISO group was higher than that in control group, meanwhile the expression of CaMKII and p-CaMKII protein was increased and the expression of CaM was decreased. Compared with ISO group, the HM/BM ratio of the peptide group decreased, and the volume of myocardial cells also decreased. The expression of CaMKII and p-CaMKII was decreased and the expression of CaM was increased. [Conclusions] In conclusion peptide-1, a new-designed peptide drug, can reduce isoproterenol-induced cardiac hypertrophy. This work was supported by the National Natural Science Foundation of China (31471091) and the Undergraduate Training Program for Innovation and Entrepreneurship (CMU2017026).