Effects of canstatin on L-type Ca^{2+} channel activity in rat ventricular cardiomyocytes

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[Background] L-type Ca^{2+} channels (LTCCs) are essential for physiological cardiac contraction. The dysfunction of LTCCs during heart failure leads to lethal arrhythmia. Extracellular matrix (ECM), a structural component in the intracellular space, regulates cellular functions. Matricryptins are bioactive fragments released from ECM, expression of which changes in the serum of chronic heart failure patients. Canstatin, a cleaved fragment of collagen type IV alpha 2 chain, is highly expressed in normal rat heart. However, the expression of canstatin decreases in the infarcted area after myocardial infarction. We have previously demonstrated that canstatin suppressed the isoproterenol-induced dephosphorylation of dynamin-related protein 1, which is regulated by Ca^{2+} /calmodulin/calcineurin pathway in differentiated H9c2 cardiomyoblasts. We tested the hypothesis that canstatin affects LTCCs in cardiomyocytes.

[Methods] Canstatin small interfering RNA (siRNA) or control siRNA with transfection reagent was injected via jugular vein in male Wistar rats. Two days after the injection, electrocardiogram (ECG) was recorded and the left ventricular tissue was isolated. The knockdown efficiency for siRNA was confirmed by Western blotting. The L-type Ca^{2+} channel current (I_{CaL}) of ventricular cardiomyocyte was measured by a whole-cell patch clamp technique.

[Results] Expression of canstatin protein was significantly decreased in the ventricle of canstatin siRNA-injected rats compared with control siRNA-injected ones. I_{CaL} of a ventricular cardiomyocyte isolated from canstatin siRNA-injected rats was significantly increased, which was reversed by treating recombinant canstatin (250 ng/ml). In ECG of canstatin siRNA-injected rats, the QT interval tended to be shortened and the amplitude of T wave was significantly increased.

[Conclusion] We for the first time clarified that I_{CaL} was increased in a ventricular cardiomyocyte where protein expression of canstatin was suppressed. It is thus suggested that canstatin might regulate the calcium-related signaling pathway in cardiomyocytes through the inhibition of LTCCs.