Impaired response to β adrenergic stimulation of L-type Ca current in ventricular cells from the SHR heart

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The hypertrophic heart muscle has been known to show a larger developed tension and a longer action potential duration as compared with the normal heart (Hart, *Cardiovasc Res* 28: 933, 1994). Although L-type Ca^{2+} current (I_{Ca}) is a major determinant of the action potential duration and Ca^{2+} release from the sarcoplasmic reticulum, several previous studies have demonstrated that its current density is not substantially different between the hypertrophic myocytes and the control myocytes. We compared the stimulatory effects of isoproterenol on I_{Ca} between the genetically-induced hypertensive rat (SHR) and control rat (WKY).

The whole-cell voltage-clamp method was employed to measure I_{Ca} on the enzymatically isolated single left ventricular cells. WKY and SHR were at 8 weeks of the age. The solutions were K^{+} -free. Test pulses were applied from a holding potential of -40 mV. In the experiments where isoproterenol was used to stimulate the I_{Ca} , the extracellular CaCl_2 concentration was reduced to 0.5 mM with MgCl_2 substituted to obtain a better voltage control. The temperature was 37°C.

Neither the current density nor the shape of the current-voltage relationship for I_{Ca} in the SHR heart cells was different from those in the WKY cells. However, the stimulatory response to isoproterenol (ISO) was diminished in the SHR cells. The maximal response (E_{max}) in response to 1 or 10 μM isoproterenol was smaller only by 15 %. Whereas, the ED_{50} was apparently higher in SHR than in WKY (70 nM for SHR vs. 20 nM for WKY). This reduced I_{Ca} sensitivity to isoproterenol in SHR heart can be ascribed to either impaired cAMP production or reduced sensitivity of Ca^{2+} channels to cAMP. Isobutyl methylxanthine (IBMX), a potent phosphodiesterase inhibitor, caused only a small accentuation of 0.1 μM isoproterenol-stimulated I_{Ca} in WKY cells. Whereas, it significantly increased the stimulated I_{Ca} by 31 ± 20 % in SHR cells ($n=5$). The % increase over the control in response to isoproterenol plus IBMX in these SHR cells was 115 ± 30 %, which was not statistically different from the E_{max} for the isoproterenol stimulation of I_{Ca} in WKY. The I_{Ca} in WKY and SHR showed comparable responses to 3 μM forskolin. These findings suggest that the cAMP producing systems including the β receptor-adenylate cyclase coupling with G protein are impaired in the SHR cells. Another possibility is that the cAMP degradation by phosphodiesterase is enhanced in the SHR heart.