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Effects of Endothelin-1 on Ca^{2+} Signaling in Guinea-Pig Ventricualr Myocytes: Role of Protein Kinase C

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Effects of endothelin-1 (ET-1) on contraction, Ca^{2+} transient and L-type Ca^{2+} current ($I_{Ca,L}$) were investigated in single ventricular myocytes isolated from guinea-pig hearts. ET-1 at concentrations of 5 and 10 nM produced a biphasic pattern of inotropism: a first decrease in contraction by 34.4±2.5 % of the control followed by a sustained increase in contraction by 66.6±8.4 % (mean±S.E.M., n=9). The Ca^{2+} transient decreased by 13.5±1.0 % during the negative inotropic phase, while it increased by 58.1±8.4 % (n=10) during the positive inotropic phase. Using the whole-cell voltage-clamp technique with conventional microelectrodes, the application of ET-1 (5 nM) increased the $I_{Ca,L}$ by 32.6±5.1 % (n=10), which was preceded by a short-lived decrease in $I_{Ca,L}$. Incubation of myocytes with pertussis toxin (PTX, at 2 g ml^{-1} for > 3 h at 35 ℃) prevented the partial Ach-induced reversal of the noradrenaline enhancement of $I_{Ca,L}$. However, an identical treatment failed to block the ET-1-induced increase of $I_{Ca,L}$ (n=8). To determine whether activation of protein kinase C (PKC) is responsible for the enhancement of $I_{Ca,L}$ by ET-1, we tested a PKC inhibitor, GF109203X, and found that it does exert an inhibitory effect on the ET-1-induced $I_{Ca,L}$ increase. Our study suggests that during ET receptor stimulation the enhancement of $I_{Ca,L}$ by PKC activation via PTX-insensitive G-protein causes an increase in Ca^{2+} transients and thereby in the contractile force of the ventricular myocytes.