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α_1-Adrenergic Effects on Intracellular Ca^{2+}, Contraction and L-type Ca^{2+} Current in Guinea Pig Ventricular Myocytes: Role of Protein Kinase C

Sun Hee Woo* and Chin Ok Lee
Dept. of Life Science, Pohang Univ. of Sci. and Tech., Pohang, Korea.

The effects of α_1-adrenoceptor stimulation on intracellular Ca^{2+} ($[Ca^{2+}]_i$) transient, contraction, and L-type Ca^{2+} current ($I_{Ca,L}$) were studied in single cells isolated from ventricles of guinea pig hearts. Phenylephrine, α_1-adrenergic agonist, ($5\times10^{-5}\sim10^{-4}$ M) produced a biphasic pattern of inotropism: transient negative response (decrease in contraction by 23.9 ± 2.5 % of control) followed by a sustained positive response (increase in contraction by 60.0 ± 3.4 %, mean ± SD, n=12). $[Ca^{2+}]_i$ transient was decreased by 10.6 ± 2.1 % during the negative phase, while it was increased by 68.6 ± 9.5 % (n=12) during the positive phase. These effects were inhibited by prazosin (10^{-6} M), α_1-adrenergic antagonist. Phenylephrine increased $I_{Ca,L}$ from 0.82 ± 0.04 to 1.31 ± 0.30 nA (by 60.8 ± 21 %, n=5).

To determine whether activation of protein kinase C (PKC) is responsible for the modulation of $[Ca^{2+}]_i$ transient, contraction, and $I_{Ca,L}$ during α_1-adrenoceptor stimulation, we tested effects of 4β-phorbol 12-myristate 13-acetate (PMA), a PKC activator, and GF109203X or staurosporine, PKC inhibitors. PMA mimicked phenylephrine effects on $[Ca^{2+}]_i$ transient, contraction and $I_{Ca,L}$. PMA (10^{-7} M) produced decreases of $[Ca^{2+}]_i$ transient and contraction by 19.8 ± 0.8 % and 26.9 ± 5.3 %, respectively, which were followed by prolonged increases of $[Ca^{2+}]_i$ transient and contraction by 133 ± 8.8 % and 139 ± 21 % (n=8), respectively. PMA (10^{-7} M) also increased $I_{Ca,L}$ from 0.77 ± 0.04 to 1.37 ± 0.32 nA (by 81.1 ± 53 %, n=5). Prior exposures to GF109203X (10^{-6} M) or staurosporine (10^{-8} M) prevented the phenylephrine effects on $[Ca^{2+}]_i$ transient, contraction, and $I_{Ca,L}$. Our study suggests that, during α_1-adrenoceptor stimulation, increase of $I_{Ca,L}$ by PKC causes an increase in $[Ca^{2+}]_i$ transient and thereby contractile force in ventricular myocytes.