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Protein kinase A mediates 8-Br-cGMP-induced Ca^{2+}-desensitization in murine aorta

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The NO/cGMP kinase pathway has prominent relaxing effects on contracted vascular smooth muscle. To elucidate to which extent Ca^{2+}-desensitization is involved in this relaxation process, experiments were performed on permeabilized aortic preparation at constant $[Ca^{2+}]$.

Both, 8-Br-cGMP (300 μM) and the Rho-kinase inhibitor Y-27632 (10 μM) relaxed contractions induced by pCa 6.5; the effects of both drugs were attenuated at higher $[Ca^{2+}]$. Interestingly, 8-Br-cGMP (300 μM) relaxed pre-contracted preparation from both wild type as well as from $cGKI^{-/-}$ mice by 78 and 58 %, respectively. Pre-treatment with the protein kinase A inhibitor peptide 5–24 reduced the 8-Br-cGMP-induced relaxation to 28 and 4 % in preparations from wild type and $cGKI^{-/-}$ mice, respectively. These results indicate that 8-Br-cGMP-induced Ca^{2+}-desensitization is mostly mediated by protein kinase A in murine aorta.

Next, we studied the effects of 8-Br-cGMP on Ca^{2+}-sensitization after stimulation of G-proteins with phenylephrine and GTP-γ-S at pCa 6.5. Phenylephrine (10 μM) did barely induce contraction at pCa 6.5, whereas GTP-γ-S initiated a strong additional contraction. In the presence of the protein kinase A inhibitor peptide 5–24, 8-Br-cGMP (300 μM) relaxed phenylephrine-induced contractions to 40 and 5% in wild type and $cGKI^{-/-}$ murine aorta, respectively. After stimulation with GTP-α-S, 8-Br-cGMP relaxed the aortic rings to about 5% in wild type, whereas Y-27632 (10 μM) induced a relaxation to about 50%.

These results show that 8-Br-cGMP-induced Ca^{2+}-desensitization is mediated by protein kinase A and cGKI. Activation of G-proteins by GTP-γ-S abolished the relaxant effect of 8-Br-cGMP but not that of the Rho-kinase inhibitor Y-27632 in murine aorta.