THE EFFECT OF CALCITONIN GENE-RELATED PEPTIDE (CGRP) ON THE CYTOSOLIC CALCIUM CONCENTRATION AND FORCE IN RAT INTRAMURAL CORONARY ARTERIES

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The aim of this study was to investigate the mechanism of CGRP-induced relaxation in intramural rat coronary arteries. By using FURA-2 technique, cytosolic Ca^{2+} -concentration ($[\text{Ca}^{2+}]_i$) was measured during contraction of the vascular smooth muscle with receptor-dependent agonist (tromboxane A_2 analogue U46619) and with high concentration of extracellular potassium. At a steady state of contraction, the increase in $[\text{Ca}^{2+}]_i$ induced by 300 nM U46619 (100 ± 14 nM, $n = 7$) was similar to that induced by 36 mM K^+ (98 ± 9 nM, $n = 7$). However, the active tension induced by 300 nM U46619 was significantly ($p < 0.01$) higher than that induced by 36 mM K^+ . CGRP concentration-dependently (10 pM - 10 nM) reduced both the $[\text{Ca}^{2+}]_i$ and tension of coronary arteries precontracted with either U46619 or BAY K 8644, and also of resting coronary arteries in PSS. In 36 mM K^+ -depolarized arteries, CGRP reduced only the tension without affecting the $[\text{Ca}^{2+}]_i$. In 300 nM U46619 precontracted arteries, pretreatment with 10 μM thapsigargin significantly ($p < 0.05$) attenuated the CGRP-induced reduction in the tension (but not $[\text{Ca}^{2+}]_i$). In 300 nM U46619 precontracted arteries, pretreatment with either 100 nM charybdotoxin or 100 nM iberiotoxin or 10 nM felodipine significantly ($p < 0.05$) attenuated the CGRP-induced reduction in both $[\text{Ca}^{2+}]_i$ and the tension. In contrast, 1 μM glibenclamide did not affect the CGRP-induced responses in these coronary arteries. In resting coronary arteries, only pretreatment with the combination of 1 μM glibenclamide and 100 nM charybdotoxin attenuated the CGRP-induced decrease in the $[\text{Ca}^{2+}]_i$ and tension, suggesting a different mechanism of action for CGRP in resting coronary arteries. We conclude that CGRP relaxes precontracted rat coronary arteries *via* three mechanisms: (1) a decrease in $[\text{Ca}^{2+}]_i$ by inhibiting the Ca^{2+} influx through membrane hyperpolarization mediated partly by activation of BK_{Ca} channels, (2) a decrease in $[\text{Ca}^{2+}]_i$ presumably by sequestering cytosolic Ca^{2+} into thapsigargin-sensitive Ca^{2+} storage sites, and (3) a decrease in the Ca^{2+} -sensitivity of the contractile apparatus.