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ROLE OF EXTRACELLULAR SIGNAL-REGULATED KINASE IN THE REGULATION OF ENDOTHELIUMDEPENDENT RELAXATIONS IN PORCINE CORONARY ARTERIES

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OBJECTIVES: Previous studies demonstrate that extracellular signal-regulated kinase (ERK) contributes to vascular contraction. The present study examined whether or not ERK modulated the different signaling pathways involved in endothelium-dependent relaxation. METHODS: Isolated porcine coronary arteries, with and without endothelium, were incubated in organ chamber for the measurement of isometric tension. They were contracted with U46619 (thromboxane A2 analogue, 30 to 100 nM) followed by cumulative additions of different relaxing agents, in the presence or absence of the ERK inhibitor, U0126. RESULTS: In the presence of indomethacin (cyclooxygenase inhibitor; 10 μM), the endothelium-dependent relaxing agent bradykinin (0.1 nM to 1 μM) induced full relaxation, in a concentration-dependent manner, in arteries, with endothelium, contracted with U46619. With addition of indomethacin plus L-NAME [nitric oxide (NO) synthase inhibitor; 100 μM), bradykininduced relaxation cannot be mediated via cyclooxygenase and NO pathways. In this condition, U0126 (10 μM) enhanced relaxation thus suggesting that ERK activation leads to inhibition of endothelium-dependent hyperpolarization (EDH) type-mediated relaxations. When EDH pathway was inhibited with TRAM-34 [intermediate conductance calcium-activated potassium channel (IKCa) blocker; 1 μM] and UCL1684 [small conductance calcium-activated potassium channel (SKCa) blocker; 1 μM], bradykininduced relaxations in the presence of indomethacin were also potentiated by U0126, thus suggesting a possible inhibitory action of ERK on the NO pathway. On the other hand, U0126 did not significantly affect relaxations to SKA-31 (IKCa and SKCa activator; 0.1 nM to 10 μM) in arteries with endothelium. As such, the inhibitory action of ERK on EDH type-mediated relaxation appears to be upstream of IKCa and SKCa activation. In arteries without endothelium, relaxations to Deta NONOate (nitric oxide donor; 0.1 nM to 10 μM) and forskolin (adenylyl cyclase activator, 0.1 nM to 10 μM) were not affected by U0126. CONCLUSIONS: Our data suggest that ERK inhibits the generation of NO and EDH in the endothelium without affecting the signaling cascades downstream of these relaxing signals in the smooth muscle. Moreover, it does not play a role in the signaling cascade downstream of adenylyl cyclase activation in the smooth muscle.