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4-aminopyridine contracts pulmonary artery in voltage-dependent and voltage-independent manner

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Voltage-gated K^+ (K_V) channels are predominantly expressed in pulmonary vasculature and have been thought to play an important role in regulation of membrane potential (V_m) and vessel contractility. The main aim of this project was to investigate the role of K_V channels in intrapulmonary arteries (PAs) isolated from male Wister rats (200-250 gm) using small vessel wire myography. Mesenteric arteries (MAs) were used as a representative of systemic circulation. Our results demonstrate that the effect of 4-AP, a specific inhibitor of the K_V channels, was significantly potentiated by 20 mM KCl that causes membrane depolarization. 4-AP-induced contraction of PAs was only partly (35.0±4%, n=6) blocked by the inhibitor of L-type Ca^{2+} channels diltiazem (10 μM), whereas in MAs contraction was nearly completely blocked (94.0±2%, n=6). Similar partial block by diltiazem was observed in PAs but not in MAs for contraction induced by 80 mM KCl. 4-AP induced contraction in PAs was also blocked by Rho-kinase inhibitor Y-27632 (10 μM). The effects of diltiazem and Y-27632 were additive in PAs. The role of Rho-kinase in 4-AP-induced contraction was confirmed with Western blot analysis. Pretreatment with 4-AP (10 μM) increased the levels of phosphorylated myosin light chain (p-MLC) in PAs. This effect was reversed by pretreatment of tissues with Y-27632 (10 μM). These results suggest that 4-AP induced contraction involves voltage-dependent and voltage-independent mechanisms and that Rho-kinase signalling pathway contributes, at least in part, to 4-AP-induced pulmonary vasoconstriction.