The nitric oxide-NO/cGMP pathway represents a major physiological signalling controlling pulmonary arterial (PA) tone and drugs activating this pathway are used to treat pulmonary arterial hypertension. Kv channels expressed in PA smooth muscle cells (PASMC) are key determinants of vascular tone. We aimed to analyse the contribution of Kv1.5 and Kv7 channels in the electrophysiological and vasodilating effects evoked by NO donors and the guanylate cyclase (GC) stimulator riociguat in PA. Kv currents were recorded in isolated rat PASMC using the patch-clamp technique. Vascular reactivity was assessed in a wire myograph. The NO donors DEA-NO and SNP hyperpolarized the membrane potential and induced a bimodal effect on Kv currents (augmenting the current between -40 to -10 mV and decreasing it at more depolarized potentials). The hyperpolarization and the enhancement of the current were suppressed by Kv7 channel inhibitors and by the GC inhibitor ODQ but preserved when Kv1.5 channels were inhibited. Additionally, DEA-NO enhanced Kv7.5 currents in COS7 cells expressing KCNQ5 gene. Riociguat increased Kv currents at all potentials ≥-40 mV and induced membrane hyperpolarization. Both effects were prevented by Kv7 inhibition. Likewise, PA relaxation induced by NO donors and riociguat was attenuated by Kv7 inhibitors. In conclusion NO donors and riociguat enhance Kv7 currents, leading to PASMC hyperpolarisation. This mechanism contributes to NO/cGMP-induced PA vasodilation. Our study identifies Kv7 channels as a novel mechanism of action of vasodilator drugs used in the treatment of pulmonary arterial hypertension.

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