Abstract

Reaction of pulmonary vascular bed to hypoxia is different than in systemic vasculature. Acute ventilatory hypoxia constricts pulmonary arteries (HPV), diverts blood to better oxygenated alveoli and optimises arterial pO_2. Chronic hypoxia causes pulmonary hypertension (HPH) and exposure to hypoxia at birth (perinatal hypoxia) results in longterm changes of pulmonary vasculature, which makes it more susceptible to develop pulmonary hypertension in adulthood. Reaction of pulmonary artery smooth muscle cells (PASMCs) to hypoxia involves membrane depolarization by inhibition of voltage gated potassium channels (Kv). Among them KCNQ (Kv7) channels have biophysical properties (low voltage threshold for activation and lack of inactivation during sustained depolarization) which suggest them to play a key role in hypoxic response.

Specific KCNQ channel inhibitor linopirdine primes HPV in saline perfused lungs, but in not primed lungs does not cause vasoconstriction, it behaves in the same way as acute ventilatory hypoxia. Moreover, in primed lungs linopirdin potentiates HPV and prevents non-specific Kv inhibitor 4-aminopyridine to potentiate HPV. It seems, that KCNQ channel inhibition has a key role in HPV.

In rats exposed to hypoxia for 3-5 days (normobaric chamber, FiO_2 0,1) we examined relationship of pulmonary perfusion pressure on increasing flow (P/Q plot). In hypoxic rats, contrary to controls, linopirdine fails to constrict pulmonary vessels. This loss on responsivness to linopirdine correlates with reduced expression of Kv7.4 mRNA in hypoxic lungs, amount of Kv7.4 protein was not affected. In contrast, KCNQ channel activator flupirtine dilates only vessels from hypoxic rats, not from normoxic controls. Moreover, flupirtine treatment during exposure to hypoxia (30 mg/kg/day) prevents increase of pulmonary vascular resistence .and normalizes response to acute hypoxia. Our results point out downregulation of Kv7.4 channels in early stage of HPH development and possibility of flupirtine to influence developement of HPH.

Changes induced by perinatal hypoxia (2 weeks in FiO_2 0,12) are more expressed in females. Adult perinatal hypoxic females have increased pulmonary vascular resistance and vasoconstriction induced by KCl. Perinatal hypoxic rats of both gender are more sensitive to linopirdine. KCNQ channels are involved in KCl induced vasoconstriction in females independently on exposure to perinatal hypoxia, but in males only if they were exposed to hypoxia at birth. KCNQ channel activity participates in different reactivity of perinatal hypoxic pulmonary vasculature and is involved in gender differences.