Effects of Verapamil and BAY K 8644 on the Hypoxic Contraction of the Isolated Human Pulmonary Artery

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OHE, M., OGATA, M., SHIRATO, K. and TAKISHIMA, T. Effects of Verapamil and BAY K 8644 on the Hypoxic Contraction of the Isolated Human Pulmonary Artery. Tohoku J. Exp. Med., 1989, 157 (1), 81-82—To examine the effect of hypoxia on the human pulmonary artery (HPA), HPA segments (2 mm, o.d.) were suspended and changes in isometric force with hypoxia (P02=44±3 mmHg, mean±s.e.) were measured. HPA contracted with hypoxia and the tension developed with 15 min of hypoxia was 127±36 (mean±s.e.) mg. Verapamil at 10⁻⁶ M inhibited and 10⁻⁶ M BAY K 8644 enhanced the hypoxic response by 47±10% (p <0.01) and 396±106% (p <0.05), respectively, compared with preceding values. These results show that activation of voltage-dependent Ca²⁺ channels also plays an important role in the mechanism of hypoxic pulmonary vasoconstriction in man.

It is well known that voltage-sensitive Ca²⁺ channels serve as a trigger in the mechanism of hypoxic pulmonary vasoconstriction (HPV) (McMurtry 1985). However, species differences are conspicuous in HPV and there are no in vitro studies of the role of voltage-dependent Ca²⁺ channels in HPV using the isolated human pulmonary artery (HPA). This is because the isolated pulmonary artery usually relaxes with hypoxia and contracts only under specific conditions. Recently, it was reported that isolated small pulmonary artery (<300 μm, o.d.) from the cat was depolarized and contracted with hypoxia (Madden et al. 1985). However, the contraction of isolated HPA with hypoxia has not been reported. The purpose of this study is to examine the mechanism of HPV in man. This is the first in vitro experimental demonstration of HPV of HPA in the resting condition.

Lung segments were obtained from patients undergoing thoracic surgery. Rings (2 mm, o.d.) were cut and suspended in Krebs-Ringer solution (37°C) with an initial tension of 3 g and changes in isometric tension were measured. During 2 hr of equilibration, they were restretched to 3 g at 30-min intervals. After an equilibration, three consecutive 15 min hypoxic challenges (P0₂=44±3 mmHg) were induced. Verapamil (Ca²⁺ antagonist), BAY K 8644 (voltage-dependent Ca²⁺ agonist) or dimethyl sulfoxide (DMSO, vehicle of BAY K 8644) were added and additional challenges were attempted. The concentrations of these agents were selected according to previous studies (Harder et al. 1985; McMurtry 1985).
Tension of HPA rings increased with hypoxia and the mean value of the tension developed by 15 min of hypoxia was 127±36 mg (s.e. n=12). The degree of HPV was unchanged by repeated hypoxic challenges. Verapamil at 10^{-6} M inhibited HPV by 47±10\% (Fig. 1, p<0.01, n=9) and 10^{-6} M BAY K 8644 markedly augmented HPV by 396±106\% (p<0.05, n=7), compared with the preceding values. DMSO at 0.3 mM did not change the degree of HPV. Fig. 2 shows a typical example of the effect of 0.3 mM DMSO and 10^{-6} M BAY K 8644 on the HPV of HPA ring.

In the present study, HPA rings (2 mm, o.d.) constricted with hypoxia and the effect of verapamil and BAY K 8644 on HPV in HPA rings was similar to that seen in other animals (Harder et al. 1985; Tolins et al. 1986). These results show that relatively larger elastic segments of HPA contract in response to hypoxia and that activation of voltage-dependent Ca^{2+} channels also plays an important role in the mechanism of HPV in man.

References