HYPOXIC PULMONARY VASOCONSTRICTION IN ISOLATED BLOOD-PERFUSED RAT LUNG; MODULATION BY THROMBOXANE A$_2$, PLATELET-ACTIVATING FACTOR, CYSTEINYL LEUKOTRIENES AND ENDOTHELIN-1

Stefan Chlopicki, Joanna B. Bartuś, Ryszard J. Gryglewski
Department of Pharmacology, Jagiellonian University Medical College, Grzegórzecka 16, PL 31-531, Kraków, Poland


Recent evidence suggests that hypoxic pulmonary vasoconstriction (HPV) is mediated by hypoxia-induced closure of voltage-gated potassium channels in pulmonary vascular smooth muscle cells. It is also claimed that various vasoconstrictor mediators such as thromboxane A$_2$ (TXA$_2$), platelet activating factor (PAF), cysteinyl leukotrienes (cys-LTs) or endothelin-1 (ET-1) contribute to HPV. Their role, however, has not been unequivocally accepted. On the contrary, it is well known that endothelium-derived nitric oxide negatively modulates HPV. Since NO counteracts action of vasoconstrictor mediators, we tested the hypothesis that modulatory role of TXA$_2$, PAF, cys-LTs and ET-1 in HPV would become apparent in absence of endogenous NO. For that purpose we assessed contribution of these mediators to HPV in the isolated blood-perfused rat lung pretreated with a non-selective NOS inhibitor, L-NAME. HPV, which was greatly augmented by L-NAME (300 $\mu$M) alone, was inhibited neither by a TXA$_2$ synthase inhibitor (Cemonagrel, 300 $\mu$M), nor by a PAF receptor antagonist (WEB 2170, 100 $\mu$M), nor by an inhibitor of five-lipoxygenase-activating protein (MK 886, 10 $\mu$M), nor by a non-selective ET-1 receptor antagonist (LU 302872, 30 $\mu$M).

In summary, in isolated blood-perfused rat lung, TXA$_2$, PAF, cys-LTs and ET-1 seem not to be involved in HPV, whereas we confirm the dominant role of endogenous NO in blunting HPV.

Key words: hypoxia, nitric oxide, pulmonary vasoconstriction, thromboxane, PAF, leukotrienes, endothelin