ABSTRACT

Pulmonary hypertension is a group of diseases characterized by increased mean pulmonary artery pressure. Especially in group 2, which is associated with heart disease and is the most prevalent of all types, and in group 3, associated with lung disease, no sufficiently effective treatment has yet been developed beyond the treatment of the underlying disease, which is problematic in many cases. Dehydroepiandrosterone sulfate (DHEA S) and statins have different mechanisms of action on pulmonary hypertension in some respects, so the question of the effectiveness of combining them on pulmonary hypertension versus either agent alone has been offered. To test this hypothesis, we induced pulmonary hypertension in adult male rats by three weeks of exposure to hypoxia (10% O2) and treated them with simvastatin (60 mg/L) and DHEA S (100 mg/L) in drinking water, either alone or in combination. Both simvastatin and DHEA S reduced mean pulmonary artery pressure (from a mean ± s.d. value of 34.4 ± 4.4 to 27.6 ± 5.9 and 26.7 ± 4.8 mmHg, respectively), but their combination was not more effective (26.7 ± 7.9 mmHg). Differences in the degree of oxidative stress (as indicated by malondialdehydedehydplasma concentration), the degree of superoxide production (electron paramagnetic resonance) or blood nitric oxide levels (chemiluminescence) did not explain the lack of additivity of the effect of DHEA S and simvastatin on pulmonary hypertension. We propose that the main mechanism of action of both drugs on pulmonary hypertension could be their inhibitory effect on 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, thus explaining the absence of additivity of their action.

The development of pulmonary hypertension may also be a side effect of drugs administered for the treatment of other diseases. One of the new types of drugs whose mechanism of action shares common elements with those of pulmonary hypertension are hypoxia-inducible factor (HIF) stabilizers being developed for use in anemias. Therefore, we tested the hypothesis that a major effect of roxadustat from this group may be pulmonary hypertension. We used isolated, cell-free, solution-perfused lungs from a rat. We found that pulmonary vascular resistance (measured as the ratio of perfusion pressure to flow) was increased by roxadustat, even after a short exposure when the effect of roxadustat on haematocrit had not yet become apparent. The risk of pulmonary hypertension with roxadustat treatment is therefore real (although not enormous) and should be monitored. Vasoconstrictor reactivity to acute hypoxic stimuli was not significantly affected by roxadustat. Thus, HIFs are probably not very involved in the mechanism of hypoxic pulmonary vasoconstriction.

Because of the high prevalence of pulmonary hypertension associated with heart disease, which is also poorly studied, partly due to the difficulty of the available experimental models, the third aim of the study was to develop and characterize a technically simple model of this type of pulmonary hypertension. The essence of the method is that the reduction of the cross-sectional area of the ascending aorta is achieved not by an external clamp (as in previous techniques requiring opening of the chest) but by partial intravascular obstruction by a mere superficial approach through the a. carotis (i.e. without opening the chest). A blinded tube is introduced by this route just above the aortic valve of the laboratory rat, where it increases the resistance in the aorta and thus the afterload of the left ventricle. We have shown that this procedure is not only relatively easy, but also that three weeks after insertion of the tube, it actually causes pressure overload in the left heart (left atrial pressure at end diastole 1.3 ± 0.2 mmHg, compared to 0.4 ± 0.3 mmHg in controls, $P<0.0001$). The presence of pulmonary hypertension was documented by measurement of pulmonary artery pressure by in vivo catheterization (22.3±2.3 vs. 16.9±2.7 mmHg, $P=0.0282$) and detection of right ventricular hypertrophy and increased muscularization of peripheral pulmonary vessels. The contribution of vasoconstriction and the pre-capillary vascular segment to increased pulmonary vascular resistance was demonstrated by normalizing resistance using the vasodilator, sodium nitroprusside, and the arterial occlusion technique in isolated lungs. Thus, intravascular partial aortic obstruction offers an uncomplicated model of pulmonary hypertension induced by left heart disease that has a vasoconstrictive and precapillary component. Thus, it is a new practical model of type 2 pulmonary hypertension with a clear precapillary component that can be used to further study the mechanisms and potential interventions for this most clinically common form of pulmonary hypertension.

Keywords

Pulmonary hypertension, statin, dehydroepiandrosterone, hypoxia-inducible factor, left ventricular overload, rat, group 2 pulmonary hypertension, heart failure with preserved ejection fraction, pulmonary vascular reactivity