Research project objectives/ Research hypothesis

Pulmonary arterial hypertension (PAH) is a complex, chronic and multi-factorial disease which leads to progressive right heart failure and death. PAH is associated with: 1) endothelial dysfunction, 2) excessive pulmonary arteries constriction, 3) vascular remodeling (smooth muscle cells proliferation and hypertrophy), 4) infiltration of inflammatory cells into the lung, 5) thrombosis and 6) increased oxidative stress. Human PAH is defined by the increase of mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg at rest. It still cannot be cured effectively, hence the search for novel treatments continues. The **monocrotaline (MCT)-induced** rat model of PAH remains a model favored by many investigators, shows a selective toxic effect on pulmonary vessels without an effect on systemic vessels and offers technical simplicity, reproducibility, and low cost compared with other models of PAH. This experimental model reminds common pathological findings in PAH in humans which were mentioned above.

The main compounds of *Cannabis sativa* var. *indica* are fitocannabinoids: tetrahydrocannabinol (Δ^9-THC) and **cannabidiol** (**CBD**). Recently, a great attention is paid to CBD, which is not psychoactive, in contrast to Δ^9-THC. Its formulated extract is the part of Sativex®, used for the treatment of pain in multiple sclerosis in adults and suggested to use in disorders of digestive system, neurodegenerative diseases and diabetes (which are connected with the increase of oxidative stress and inflammatory response). In a few studies, the beneficial cardioprotective as well as vasorelaxant properties of CBD were described. CBD leads to indirect relaxant effects in isolated human mesenteric and pulmonary arteries and rat aorta. In model of stress, acute CBD administration significantly reduces the increase in blood pressure in patients. Incubation with CBD increases relaxant potency of rat aorta both in primary and secondary model of hypertension. Besides indirect hypotensive properties of CBD, it exerts protective effects, e.g.: 1) in vascular endothelium, retina and heart in diabetes; 2) in the reduction of the vascular hyperpermeability in cerebral arteries treated with lipopolysaccharide 3) and in heart and cerebral arteries in the model of ischaemia. The improvement of lung function in the murine model of septic shock- induced lung injury by CBD suggests its possible beneficial effects also in the treatment of inflammatory lung diseases.

Taking into account the prevalent favorable properties of CBD (in systemic and pulmonary vasculature), the aim of this project is the comprehensive evaluation of potentially protective effects of CBD in the rat experimental MCT-induced model of PAH. We are planning to examine the chronic influence of CBD on isolated pulmonary arteries, hemodynamic parameters as well as particular parameters of oxidative stress, inflammation and hemostasis (Figure 1).

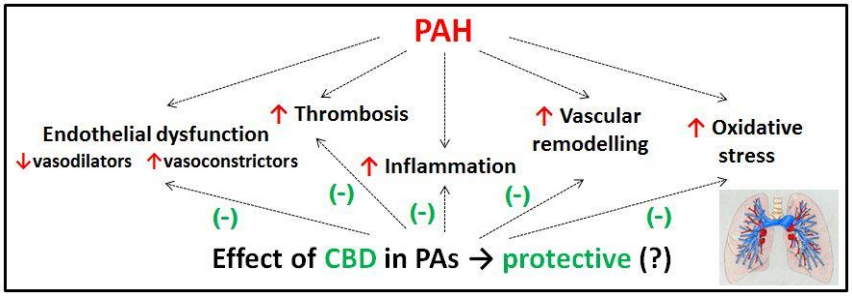

Fig.1. The suggested protective effects of cannabidiol (CBD) in the model of pulmonary arterial hypertension (PAH). PAs – pulmonary arteries.

Research project methodology

All experiments will be performed on Wistar rats. We will create 6 groups: 3 groups without PAH (1-control, 2-solvent and 3-CBD), and three with MCT-induced PAH (4-control, 5-solvent and 6-CBD). To prevent the pulmonary alterations elicited by MCT we have chosen the prevention protocol in which rats will receive CBD (10 mg/kg) or its vehicle intraperitoneally once daily for 4 weeks since MCT injection. Day after the last dose of CBD, 1) the alterations in right ventricle blood pressure will be measured, 2) the relaxant-constrictor effects in isolated pulmonary arteries will be investigated and 3) in collected hearts, lungs and arteries the morfometric changes with respect to selected assays of oxidative stress, inflammation and hemostasis will be also performed.

Expected impact of the research project on the development of science, civilization and society

Proposed project is basic research which for the first time undertake the issue of the chronic influence of CBD not only in MCT-induced model of PAH but also under physiological conditions in pulmonary vascular bed. Our studies will extend the basal knowledge about the various positive and/or negative (potential side effects) effects of CBD on oxidative stress, inflammation and hemostasis. Understanding the chronic effects of CBD in preclinical studies is a rational first step for clinical studies and for future research of this compound. The possibility of introducing new treatment for still incurable PAH would appear. Moreover, our project might add strictly scientific facts to the emotional discussion about the legalization of medical marijuana.