

## Rozprawa Doktorska/ Doctoral Thesis

**Tytuł: Ocena wpływu kannabidiolu na parametry zapalne i włóknienia w tkance płucnej i prawej komorze serca w szczurzym modelu nadciśnienia płucnego indukowanego monokrotaliną**

**Title: Evaluation of the effects of cannabidiol on inflammatory and fibrosis parameters in lung tissue and right ventricle in a rat model of monocrotaline-induced pulmonary hypertension**

**Autor/Author: mgr Anna Krzyżewska**

### Summary

**Pulmonary hypertension**, defined as when mean pulmonary artery pressure is above 20 mmHg, is an incurable disease with a multifactorial etiology. The pathogenesis of PH involves endothelial dysfunction of pulmonary vessels leading to their excessive contraction and remodeling, increased inflammation and oxidative stress. The result of above-mentioned changes is increased resistance in the pulmonary circulation, increased afterload, hypertrophy and fibrotic changes of the right ventricle, its failure and premature patients' death. Current therapies do not fully cure the disease and cover mostly pulmonary vasorelaxation. It is suggested that the best therapeutic strategy for treating pulmonary hypertension is early polytherapy targeting several points of resolution including reducing vascular resistance in the pulmonary circulation, as well as anti-inflammatory, antioxidant, and anti-fibrotic effects.

**Cannabidiol (CBD)** is one of the best researched constituents of *Cannabis sativa*, with no psychoactive effects and a high safety profile. Cannabidiol has wide range of beneficial properties including anti-inflammatory, antioxidant, anti-fibrotic and vasorelaxant effect on pulmonary vessels.

Therefore, **the aim of the study** was to evaluate the effect of CBD on inflammatory and fibrotic parameters in lung tissue and/or right ventricle in a rat model of pulmonary hypertension (PH) induced by the plant alkaloid monocrotaline (MCT) with a simultaneous analysis of the usefulness of cannabinoids in adjuvant therapy for PH treatment.

The experiments were performed on tissues collected from rats with MCT-induced PH (single, subcutaneous injection, 60 mg/kg). Cannabidiol (10 mg/kg) or its solvent was administered intraperitoneally for 21 days after MCT injection. In the studies I used biochemical (including Western Blot, ELISA) and histological (including immunohistochemical staining) methods.

The lungs of rats with MCT-induced PH showed a decrease in total antioxidant capacity (TAC) and glutathione (GSH) levels, an increase in inflammatory mediators: tumor necrosis

factor alpha (TNF- $\alpha$ ), interleukin 1 beta (IL-1 $\beta$ ), nuclear factor kappa B (NF- $\kappa$ B), monocyte chemoattractant protein-1 (MCP-1) and cluster of differentiation 68 (CD68), as well as cannabinoid receptors CB<sub>1</sub> and CB<sub>2</sub>. The rats' right ventricles showed an increase in the levels of parameters related to its dysfunction and profibrotic parameters including: N-terminal pro b-type natriuretic peptide (NT-proBNP), cardiomyocyte width, area of interstitial and perivascular fibrosis, number of fibroblasts and immunoexpression of fibronectin, as well as levels of transforming growth factor beta 1 (TGF- $\beta$ 1), galectin-3 (Gal-3), SMAD2, pSMAD2 and alpha-smooth muscle actin ( $\alpha$ -SMA). On the contrary, VE-cadherin (a marker of endothelial cells) level was reduced. Chronic CBD administration increased the levels of TAC and GSH and decreased the levels of CB<sub>1</sub> receptors and the factors: TNF- $\alpha$ , IL-1 $\beta$ , NF- $\kappa$ B, MCP-1 and CD68. Cannabidiol also reduced plasma NT-proBNP concentrations, cardiomyocyte width, area of fibrosis, immunoexpression of fibronectin and fibroblast amount, as well as the levels of TGF- $\beta$ 1, Gal-3, SMAD2, pSMAD2 proteins and increased VE-cadherin levels in the right ventricles of rat.

**In summary**, my own research shows pleiotropic beneficial effects of CBD including antioxidant and anti-inflammatory in lung tissue and anti-fibrotic in the right ventricle of rats with MCT-induced PH. Above mentioned effects combined with pulmonary vasorelaxant effects, as summarized in the in the review paper, suggest that CBD fits in with current trends as an adjuvant therapy for pulmonary hypertension treatment.

Anna Krzyżewska 22. 04. 2024r.