Summary

Arterial (systemic) and pulmonary hypertension (PH) are multi-factorial, high-pressure disorders. The first one is a civilizational disease, the second one is characterized by a very high mortality rate. Among many others, (endo)cannabinoids recognized for their strong vasorelaxant properties are suggested as possible drugs for various types of hypertension.

The aim of my dissertation was an evaluation of the influence of chronically administered (1) cannabidiol (CBD) in primary and secondary arterial hypertension and (2) the peripheral CB_1R antagonist JD5037 alone or combined with the AMPK activator metformin in PH. Additionally, I have reviewed available literature on (endo)cannabinoids in systemic and pulmonary hypertension, which helped me to determine if those compounds can be used as effective anti-hypertensive drugs.

I have performed all experiments on two rat models of systemic hypertension: spontaneously hypertensive rat (SHR; primary) and deoxycorticosterone acetate (DOCA)-salt (secondary) model, and rat monocrotaline (MCT)-induced model of PH. In arterial hypertension, I have not observed the effect of 2-week chronic administration of CBD on blood pressure (BP), heart rate or body weight. There were, however, some alterations to other parameters. In hypertensive animals, CBD decreased fatty acid amide hydrolase (FAAH) activity, diminished lipid peroxidation and lowered model-dependently levels of endocannabinoids with vasodilatory properties. What is more, in normotension, it increased lipid peroxidation and acted as an FAAH activator.

In PH, monotherapy with JD5037 resulted in partial reverse of fibrotic/inflammatory alterations in cardiac tissue. Metformin alone possessed similar effects, but it also decreased right ventricular systolic pressure (RVSP) and increased oxygen saturation. The strongest activity was, however, observed when JD5037 was combined with metformin. Combined therapy decreased RVSP, right ventricle hypertrophy and increased blood oxygen saturation. It also tended to reduce pulmonary vascular thickness.

The most striking finding of the review paper is the difference in the action of the (endo)cannabinoids based on their target specificity. Multitarget compounds were not effective as anti-hypertensive drugs in arterial hypertension, since they induce responses leading to both a decrease and an increase in BP. In PH, both multi- and monotarget (endo)cannabinoids were found effective.

In summary, my original research both with literature review showed that: (1) contrary anti- and pro-hypertensive effects of chronic CBD administration result in failure of BP decrease in experimental models of primary and secondary hypertension in rats; (2) chronic 21-day combined administration of metformin and JD5037 attenuated most of the mild PH-induced cardiopulmonary alterations and tended to be more efficient than any of the monotherapies alone; and (3) monotarget (or target-specific) but not multitarget (endo)cannabinoids are effective and should be further studied as anti-hypertensive drugs in systemic hypertension, but both of these groups can be successfully used in PH.