The mechanisms of hypotensive effectiveness of a stable analogue of 14, 15-epoxyeicosatrienoic acid: EET-A.

According to the World Health Organization in 2013 around 22% of the world's population suffered from hypertension (systolic blood pressure >140 and diastolic blood pressure >90 mmHg) and in developed countries it affects more than 30% of people. Moreover, 26% of people were diagnosed with pre-hypertension. Hypertension can lead to blood circulation disorders, damage of organs, such as heart or kidneys, and many other complications, like stroke, heart attack, kidney failure, which quite often are fatal. The prevalence of hypertension is lately referred to as the global epidemic of the XXI century. The financial outlay for the treatment of hypertension and related complications in Poland alone approximates 30 milliard PLN annually. Arterial hypertension can be characterized by the concomitant occurrence of various pathologic phenomena, such as (**i**) structural damage of blood vessels and/or impairment of their functions, as a result of impaired synthesis and release of vasodilator agents. (**ii**) hyperactivity of the nervous system (especially of its sympathetic axis, associated with body stimulation and stress), (**iii**) enhanced harmful oxidative stress and (**iv**) chronic inflammation of low intensity. All of the above-mentioned phenomena can be both the cause and a consequence of hypertension. Kidney plays the crucial role in the pathomechanism of hypertension, as an organ responsible for regulation of body fluids composition and volume, it maintains the blood pressure on the appropriate level.

Numerous active substances synthesized in the kidneys affect structure and function of blood vessels, renal water and sodium excretion and sympathetic nerve activity. It should be emphasized that the kidney may be the cause (source), but also the victim of hypertension. Over the years various strategies were developed to combat hypertension. Nonetheless, there is still a great need for new hypotensive drugs, especially for the treatment of resistant hypertension, which usually requires administration of drugs from different categories, which is always burdensome to the patients. Research conducted in our Department, also performed together with the foreign Partner, has long been focused on finding new antihypertensive strategies and new sites of drug action. After detailed analysis of the processes accompanying or being even the cause of hypertension, we postulate that these processes could be prevented or repaired by elevated level of epoxyeicosatrienoic acids (EETs), the metabolites with documented vasodilatory, diuretic and natriuretic activity. Moreover EETs facilitate the production of vasodilatory nitric oxide, augment the function and integrity of the vascular endothelium, exhibit antioxidant activity and inhibit inflammation. All of the above-listed properties of EETs could therefore contribute to reduction of blood pressure in patients with hypertension and translate into improvement of functions of the kidneys and cardiovascular, system, both crucially involved in the pathogenesis of hypertension.

The aim of this project is to establish whether administration of stable analogue of 14,15-EET (EET-A) will prevent the development of hypertension in young, spontaneously hypertensive rats (SHR) and/or if it will decrease the blood pressure in older SHRs in the established phase of hypertension. The course of hypertension development in SHR is characterized by the presence of most of negative features observed in patients with essential hypertension. We plan to investigate the impact of EET-A on all the above-mentioned processes related to hypertension. Also we want to determine alteration of which of those processes/mechanisms would be the most crucial for antihypertensive therapy.

Rats will receive EET-A in drinking water (for four weeks) or its solvent (drinking water) as a control. In the chronic phase of study blood pressure will be measured; urine and blood samples will be analysed for signs of kidney damage, oxidative stress and inflammation. After chronic observation anaesthetised rats will be subjected to diverse experimental procedures, in order to elucidate the relationships between vascular reactivity to vasoactive agents, bioavailability of vasodilating substances, oxidative stress and the role of renal nerves. This will be followed by examination of various organs (heart, kidneys, aorta) for morphological analysis; some of unique determinations will be conducted in Partner lab. The research should help understand the pathomechanisms of hypertension and the role of crucial processes leading to elevation of blood pressure. Hopefully, based on the expected results we will be able to offer new therapeutic approach to fight the disease.

The cooperation with the foreign Partner will provide the learning opportunities for the team members and give the chance to introduce state of the art methodology to our Laboratory. The Partnership will create the comprehensive and unique platform to exchange knowledge and experience, augmenting the status of the both teams internationally.