Cannabinoids were originally derived from *Cannabis sativa* and are responsible for the psychoactive and medicinal properties of its preparations (marijuana, hashish). They acts mainly via cannabinoid receptors (CB_1 and CB_2). Human and animals also synthesize compounds having affinity for these receptors – the so-called **endocannabinoids** (ECBs). The best known ECBs are anandamide (AEA) and 2-arachidonyl glycerol (2-AG). They are degraded by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively. These elements form endocannabinoid system, which affects many physiological functions, including the activity of the cardiovascular system. In various pathophysiological conditions ECB system is up-regulated, what may serve as a compensatory mechanism. Thus, the increase in ECB tonus e.g., by inhibiting their degradation, represents a promising therapeutic approach in a variety of disease to overcome serious central side effects of exocannabinoids.

It is suggested that up-regulation of ECB observed in **hypertension** system may be a pathophysiological response buffering increases in blood pressure. Hypertension is the most common cardiovascular risk factor contributing to widespread morbidity and mortality worldwide. About 90% of hypertension cases are classified as primary hypertension, where the precise cause is unknown. Oxidative stress and inflammation play a critical role in the pathogenesis of hypertension and its long-term complications. Thus, hypertension, oxidative stress and inflammation are involved in a self-perpetuating vicious cycle which culminates in progressive target organ injury and dysfunction (see Ryc.1). ECBs can affect all these elements.

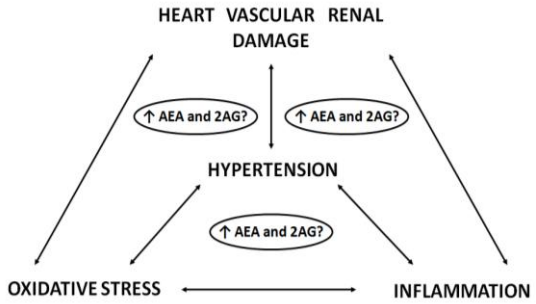

Fig. 1. Cross-talk between hypertension, oxidative stress, inflammation and organ damage.

The results of preclinical investigations with the acute administration of the FAAH inhibitors suggest their potential role as antihypertensive agents. The effects of chronic FAAH inhibition on various cardiovascular parameters, oxidative stress and inflammation in normotensive and hypertensive rats are age- and model-dependent and in some aspects may be beneficial. The therapeutic potential of MAGL inhibitors in hypertension is still entirely unknown. The full spectrum of ECB activities is not observed upon inhibition of either FAAH or MAGL enzymes or genetic deletion of either FAAH or MAGL alone and the crosstalk between distinct AEA- and 2-AG-regulated effects has been suggested in recent studies. **Thus, the aim of our project is to examine the influence of the dual FAAH and MAGL inhibition on the cardiovascular system, oxidative stress and inflammation in hypertensive and normotensive (control) rats, i.e. rats with higher and physiological endocannabinoid tone, respectively.**

All experiments will be performed on the experimental model of primary hypertension (the main form of hypertension in human) – spontaneously hypertensive rats (SHR) and their respective normotensive controls. In our experiments we will use the best known **dual FAAH/MAGL inhibitor JZL195**. We will examine its effects both after single and chronic administration on the cardiovascular system (including the function of the isolated heart and vessels) and the components of ECB system. In addition, we will study the influences of chronic JZL195 treatment on histological changes in organs and parameters of oxidative stress and inflammation.

The planned project is intended to be the first to thoroughly examine effects of dual blockade of FAAH and MAGL on the cardiovascular system, oxidative stress and inflammation under physiological (normotensive rats) and pathological (hypertensive rats) conditions. Simultaneous application of cardiovascular functional studies (both *in vivo* and *in vitro*) and analytical, biochemical and histological techniques will allow a comprehensive examination of the antihypertensive potential of dual FAAH/MAGL inhibitors. In addition, the investigation of their influence on oxidative stress and inflammation (two basic elements of the pathogenesis of many diseases) will help to establish the therapeutic potential of this group of compounds. Moreover, the complex examination of the effects of chronic blockade of endocannabinoid degradation in normotensive animals will extend our knowledge about the various positive and negative (potential side effects in other indications) effects of dual FAAH/MAGL inhibitors. It is very important in the light of recent discontinuation of clinical trial in France related to FAAH inhibitor due to occurrence of serious adverse events (including death of one of them) in the participating subjects in January 2016.