# ABSTRACT

Both sympathoneural and sympathoadrenal systems are involved in the regulation of arterial blood pressure and in the pathogenesis of hypertension. Spontaneously hypertensive rats (SHR), the mostly used animal model of genetic hypertension, is characterized by multiple molecular, morphological and functional alterations at different levels of sympathoneural and sympathoadrenal systems. The study of young prehypertensive SHR allows to reveal the abnormalities preceding hypertension development, whereas adult SHR with established hypertension offers a better model for the treatment of human essential hypertension. The aim of my PhD Thesis was to describe abnormalities in sympathoneural and sympathoadrenal systems in SHR under different conditions. Firstly, ontogenetic differences which might contribute to hypertension development were determined. Secondly, the effect of chemical sympathectomy induced by guanethidine in adulthood on cardiovascular parameters and on the compensatory mechanisms counteracting the reduction of blood pressure were studied. Thirdly, stress-induced cardiovascular response and stress-induced changes of sympathoneural and sympathoadrenal systems were described in adult SHR. My Thesis brought several important results. The increased adrenal catecholamine content and the increased density of sympathetic innervation observed in prehypertensive SHR compared to age-matched normotensive WKY rats could be involved in the pathogenesis of high blood pressure. The downregulation of the expression of genes involved in catecholamine biosynthesis (*Th*, *Ddc*, *Dbh*, *Pnmt*) is probably a compensatory mechanism counteracting the hyperfunction of the sympathoneural system. The suppression of catecholamine biosynthesis develops concurrently with the progress of hypertension in SHR. It results in the lower catecholamine content in the adrenal glands but not in the lower vascular sympathetic innervation of adult SHR. A greater role of sympathetic nervous system in blood pressure maintenance was documented in adult SHR compared to WKY rats. However, chronic sympathectomy by guanethidine is not an effective method for pernament blood pressure lowering in adult SHR with established hypertension. This might be explained by the involvement of compensatory mechanisms in sympathectomized rats, such as

the enhanced blood presure sensitivity to catecholamines and the increased plasma levels of adrenaline. Adult SHR showed an exaggerated cardiovascular response and excessive activation of sympathoneural and sympathoadrenal systems during the acute restraint compared to WKY rats. Furthermore, SHR subjected to restraint exhibited the overactivation of hypothalamic-pituitary-adrenal axis which might intensify sympathetically mediated rise in peripheral vascular resistance and stress-induced cardiovascular response. In line with sympathetic hyperactivity, a greater elevation of mRNA expression of *Th* gene was observed in the adrenal medulla of stressed SHR compared to WKY rats. In contrast, the mRNA expression of other genes involved in catecholamine biosynthesis (*Ddc*, *Dbh*, *Pnmt*) was lower in adrenal medulla of stress-naive as well as stressed SHR in comparison to WKY. This finding suggests the involvement of other mechanisms in the regulation of these enzymes. The possible cause might be a lower stimulation of adrenal chromaffin cells by angiotensin II resulting from the attenuated plasma renin activity and the decreased mRNA expression of adrenal angiotensin II receptors observed in SHR. In conclusion, the data presented in my PhD Thesis confirmed that the sympathetic nervous system contributes to the development and maintenance of high blood pressure in SHR. Its effects on cardiovascular system might be potentiated by the excessive activation of hypothalamic-pituitary-adrenal axis observed in this rat strain. Similar mechanisms are involved in the development and maintenance of high blood pressure in humans. Therefore, the investigation of abovementioned phenomena in SHR can contribute to a better understanding and treatment of human essential hypertension. The resistance of adult SHR to the treatment targeting the peripheral sympathetic nervous system can provide an insight into the compensatory mechanisms which counteract the effective treatment of high blood pressure. Therefore, the drugs affecting central regulation of cardiovascular system (e.g. ACE inhibitors or angiotensin receptor blockers) might be better for the effective lowering of blood pressure in hypertension.