

Abstract

Within the span of few decades, there has been a significant increase in diabetes mellitus and chronic stress in developed countries, such as the Czech Republic. These conditions have a significant negative effect on physical and mental health. Repeated and long-term exposure to raised levels of glucose, overactivity of the sympathetic nervous system and the increase in plasma levels of stress hormones affects most of the organs in the body, including the heart. The cardiovascular system is regulated by a broad number of neurotransmitters, hormones and neuropeptides. Alterations in the innervation of the cardiovascular system, as a result of both diseases, can affect its physiological functions.

The present thesis focuses not only on the role of the classic, but primarily on the peptidergic innervation of the heart. The aim was to contribute to the explanation of the impact of neuropeptides and their shared receptor systems on the genesis and the development of heart damage due to diabetes mellitus and/or exposure to stressors. Knowledge of the physiological characteristics of neuropeptides and their involvement in the pathogenesis of both diseases and related complications could be helpful in determining the optimal treatment method or alternatively allow us to use the cardio protective effect of neuropeptides.

The first section is focused on the impact of experimentally induced diabetes on the sensory innervation of the rat heart, which participates in the transmission of pain impulses. We studied changes in the expression of the signal system of adrenomedulin/calcitonin gene-related peptide (CGRP). Our results suggest that insufficiency of the heart sensory system is not probably caused by a dysfunction of the CGRP signaling system. We have not shown a decrease in expression of involved mRNAs due to chronic diabetes in rats. Sensory fibres in the heart except for CGRP release substance P (SP), and therefore we focused on the study of gene expression of substance P and the NK1 receptor. Our results indicate that in the atria there are significantly higher amounts of mRNA and protein of this receptor in comparison to the ventricles. The reason may be in the presence in some neuronal bodies of the intracardiac ganglia, suggesting that SP may be involved in the activity of the intracardiac nervous system.

The second part deals with the influence of different types of stress on cardiac innervation in rats. In experimental work, we used two strains of rats: control Sprague-Dawley (SD) and Lewis (LE), a strain with genetically determined reduced reactivity of the HPA axis. We investigated the effect of different types of stress on

the expression, and possibly distribution of tyrosine hydroxylase enzyme genes (TH) and choline acetyl transferase (ChAT) simultaneously with the M₂ receptors.

We found that the level of gene expression of enzymes responsible for the synthesis of classical transmitters norepinephrine and acetylcholine in individuals of both strains differ significantly. Higher expression of mRNA for TH was noted in subjects of strain LE in the atria, which are localized the neuronal bodies of intracardiac nervous system in the rat. The same applies to the type M₂ cholinergic receptors. The exception is the mRNA expression of ChAT in the right atria, which is higher in SD-strain rats than in LE subjects.

Another important peptide that is produced and released in the heart and is regarded to the regulation of the cardiovascular system, atrial natriuretic peptide. Also, its expression in individual from strain LE was significantly higher than in SD rats. In studying gene expression of the oxytocin receptor we were observed in the right atrium a significant difference between individuals of both strains in response to acute stress. While in the strain SD, relative gene expression increased, at LE we found a significant decrease. Analogous results were observed in the right atrium and in determining expression of mRNA for ANP. These results show that the level of activity of HPA axis during stress affects the expression of genes in the heart.