ABSTRACT

Ischemic heart disease is the leading cause of death and disability worldwide. The effects of ischemic heart disease are usually attributable to the detrimental effects of acute myocardial ischemia/reperfusion (I/R) injury. The aim of the thesis was to contribute to current effort to clarify the basis of mechanisms that could save the heart from I/R injury.

The whole thesis is based on four studies; while the first three are published, the fourth one has been under revision. In the first study, we proved the involvement of nitric oxide (NO) in the cardioprotective mechanism of chronic hypoxia (CH). We described that exogenously increased availability of NO as well as inhibition of phosphodiesterase type 5 led to increased myocardial tolerance of normoxic and chronically hypoxic rats. The effects of both interventions were not additive, suggesting that NO is included in cardioprotective signaling of CH. Second study continued in investigating molecular mechanisms underlying cardioprotection induced by CH. We showed that infarct size-limiting effect of adaptation to CH was accompanied by increased myocardial concentration of tumor-necrosis factor alpha (TNF-α) and TNF-α receptor R2. In the third study, we examined the effect of dexrazoxane (DEX), the only clinically approved drug against anthracycline-induced cardiotoxicity, on I/R injury. We found a narrow dose range that could supress ischemic and reperfusion arrhythmias in isolated perfused hearts, while only the highest dose of DEX reduced infarct size in open-chest rats. Surprisingly, DEX-mediated cardioprotection was not associated with the decrease in oxidative stress, which had been believed as a major cause of anthracycline-induced cardiotoxicity as well as I/R injury. In the last study, epoxyeicosatrienoic acid analog exhibited neither cardioprotective nor blood pressure-lowering effect in two-kidney, one-clip Goldblatt hypertensive rats, a model resembling human renovascular hypertension. Unexpectedly, we found an infarct size-limiting effect in untreated hypertensive rats.

In conclusion, this thesis provided new findings in the field of experimental cardiology. We examined components of molecular signaling pathways leading to cardioprotection provided by CH and described the effects of exogenous drugs with possible beneficial impact on the ischemic myocardium. All these findings could be useful for development of new strategies for protecting the heart against acute I/R injury.