Abstract

It has recently been discovered that the effect of morphine can significantly reduce the tissue damage that occurs during myocardial ischemia. The molecular mechanisms by which morphine acts on the heart are still little understood. The aim of this thesis was to monitor the effect of chronic 27-day and 10-day administration of low (1 mg/kg/day) and high (10 mg/kg/ day) doses of morphine on the expression of selected G-protein-coupled receptors (GPCR) and on the expression and activity of adenylyl cyclase (AC).

Chronic (27 days) morphine treatment reduced the expression of κ-opioids receptors, but 10-day morphine exposure did not influence the expression of these receptors. Assessment of β_1- and β_2-AR by immunoblot technique did not show any significant change in the expression, but the more accurate determination of β-AR expression using the saturation binding studies revealed that 27-day treatment with high doses of morphine appreciable increased the total number of these receptors. Administration of high doses of morphine led to marked up-regulation of adenylyl cyclase (AC) isoforms V/VI, and the amount of AC decreased proportionally with the time of discontinuation of morphine administration. Low doses of morphine up-regulated AC only during 27-day administration. Chronic morphine exposure did not affect the basal aktivity of AC however, it increased the stimulated AC aktivity and reduce the inhibitory effect of activated Gi subunits on the enzyme activity.

Our results indicate that chronic morphine exposure has significant effect on the expression of AC V/ VI and does not induce any change in the amount of opioid receptors in the cytoplasmic membrane. Chronic morphine administration appears to affect myocardial β-adrenergic signaling system and leads to upregulation of the stimulatory pathways and downregulation of the inhibitory pathways affecting the activity of AC.

Keywords: morphine, G-protein coupled receptors (GPCR), opioid receptors, β-adrenergic receptors, adenylyl cyclase