2. Abstract

The aim of this dissertation was to study the expression of proteins that participate in apoptosis in myocardium of rats treated with low (0,1 mg/kg; 1 mg/kg) and high (10 mg/kg) doses of morphine. Low doses of morphine were administered daily for 28 days and high doses for 10 days. In addition, the effect of one week of drug withdrawal was studied in animals administered 1 mg/kg of morphine. Another aim was to determine activity of caspase-3 in samples of rat myocardium prepared from control rats and those exposed to high dose (10 mg/kg) of morphine for 10 days.

The balance between cell division and cell death is crucial for the maintenance of homeostasis. Apoptosis is controled by proteins from the Bcl-2 family. These proteins are able to regulate permeability of outer mitochondrial membrane and may facilitate the release of cytochrom c and other proteins from mitochondria under certain conditions. The release of these proteins then leads to activation of executive enzymes of apoptosis. In this thesis we investigated the expression of proapoptotic proteins AIF, Bax, Bak, Bid and antiapoptotic protein Bcl-2 in samples from left myocardial ventricles of rats that was treated with different doses of morphine. Except for a significant decrease in the expression of AIF after short-term treatment with a high dose of morphine, there were no changes in the expression of the other proapoptotic proteins. The expression of antiapoptotic protein Bcl-2 was significantly increased after long-term morphine treatment using a dose of 0,1 mg/kg/day. Caspase-3 and its p11 subunit were other proteins that were identified in myocardial samples. In both cases significant differences were observed after treatment of morphine using a dose of 1 mg/kg/day for 28 days followed by one week of drug withdrawal. Whereas there was no significant difference in the expression of Akt 1/2/3, an increased expression of GSK-3β was detected in samples from animals affected by long-term treatment with low dose of morphine (1 mg/kg/day for 28 days) followed by one week of drug withdrawal.

Caspase-3 belongs to the most important effector caspases. The activity of caspase-3 was measured using the fluorescent substrate N-Ac-DEVD-N´-MC-R110 in samples from the left and right ventricles of rats treated with high dose of morphine. Morphine exposure resulted in somewhat decreased activity of this enzyme. It can be concluded that, under these conditions, morphine may elicit cardioprotective effects.

Keywords: apoptosis, caspases, morphine, myocardium