Summary

Only a small attention was paid for long time to reducing enzymes, but today it is clear that these are an important part of the endogenous metabolism and also the phase I biotransformation of xenobiotics. The significant group of reducing enzymes are carbonyl reductases that belong to two superfamilies – short chain dehydrogenases/reductases (SDR) and aldo-keto reductases (AKR). Their role in cancer is now intensively studied and their functions in cancer it is possible to divide into two main sections.

It is known that carbonyl reductases play a substantial role in hormone-dependent cancers as prostate, breast or endometrial cancer. Active estrogens or androgens are important growth factors for these cancers because they evoke increasing of cell proliferation so that elevated possibility of mutations of important genes and development of cancer. Carbonyl reductases along with other enzymes (e.g. aromatase) participate in formation of these active sex hormones in extragonadal tissues, so an inhibition of such enzymes may be a target of anticancer therapy of hormone-dependent cancers. It is necessary to determine which enzymes are essential for the formation of active sex hormones in particular types of cancers. Besides hormone-dependent cancers, carbonyl reductases play also role in cancers that have not sex hormones as growth factors. This area is only poorly understood in comparison with hormone-dependent cancers and just recently some information appears. It was proved that enzyme AKR1C3, besides metabolism of sex hormones, also takes part in metabolism of prostaglandins and generates such types of prostaglandins that affect cell signalization to increase of cell proliferation. Carbonyl reductases also contribute to the metabolism of retinoic acid which is essential either for correct embryonic development or differentiation of adult tissues. Its concentration is carefully maintained and many different enzymes, including reductive retinol dehydrogenases, participate in its metabolism. All alterations in expression or activity of these enzymes can lead to decrease of level of retinoic acid resulting in dedifferentiation of tissues and possibly in cancer progression. Besides retinol dehydrogenases from SDR superfamily also AKR1B10 probably play an important role in this mechanism.

The second mechanism, by which carbonyl reductases are involved in cancer, is their role in phase I biotransformation of carcinogens and anticancer drugs. Various carbonyl reductases participate in deactivation of the most potent tobacco-specific carcinogen NNK and also activated form of aflatoxin B1 (aflatoxin B1 dihydrodiol), thereby protect cell from a formation of NNK or aflatoxin B1-induced tumors. Carbonyl reducing enzymes play a role in biotransformation of clinically used cytostatic drugs doxorubicin and daunorubicin and potential anticancer drugs oracin and benfluron. The reduction of carbonyl groups of these

drugs leads to their inactivation and may be connected with resistance of cancer cells to doxorubicin or daunorubicin anticancer therapy.

The aim of this doctoral thesis „The role of reductases in cancer“ is possible to divide into two parts as well as mechanisms of action of carbonyl reductases in cancer. The aim of the first part is to find a potent inhibitor of the enzyme AKR1C3 that probably acts as an important contributor to development of hormone-dependent cancers of prostate or breast. The goal of the second part is purification and characterization of new microsomal carbonyl reductase(s) participating in metabolism of anticancer drug oracin and probably other carbonyl xenobiotics. Both aims have been successfully fulfilled and results contribute to the knowledge of both mechanism of action of carbonyl reductases in cancer.

It has been found a potent inhibitor of AKR1C3 – 2´-hydroxyflavone with very low IC_{50} = 300 nM. This inhibitor is selective to only AKR1C3 enzyme, from the group of AKR1C subfamilyand therefore it is a good potential for clinical use in a therapy of hormonedependent

cancers of prostate or breast. Moreover, it has been discovered that 7-hydroxyflavone is more potent inhibitor of AKR1C1 than AKR1C3. The value of IC_{50} = 75 nM points to possible use in a treatment of hormone-dependent endometrial cancer where AKR1C1 plays an important role. Alongside it, a new microsomal carbonyl reductase participating in metabolism of anticancer drug oracin has been partly purified and characterized. Its kinetic parameters for reduction of oracin have been determined and compared with kinetic parameters of reductases that participate in metabolism of oracin. It can be concluded that the new microsomal carbonyl reductase will probably play very important role in metabolism of oracin when its kinetic parameters are compared with others already published. Most likely the new enzyme will also contribute to the metabolism of other similar carbonyl drugs as antracycline cytostatic drugs doxorubicin and daunorubicin, and possibly play a role in resistance of cancer cell to antracycline therapy. This project achieves entirely new results, because only one known microsomal carbonyl reductase yet that takes part in metabolism of xenobiotics is 11･ -HSD1. Due to these reasons it is imperative to isolate and identify the new microsomal carbonyl reductase by mass spectrometry in near future.