

The liver is the major organ determining the amount of drugs reaching target organs in the human body (bioavailability) after oral administration, due to its key role in the metabolism of drugs, provided by enzymes participating their metabolism, i.e. drug metabolizing enzymes. Activity of those enzymes, in co-operation with function of drug transporters located in cell membranes of hepatocytes that shift medications, constitutes principal determinants of quantity of active drug molecules reaching target organs.

Proper function of drug metabolizing enzymes localized in the liver is therefore extremely important to ensure their proper metabolism and elimination from the body. Furthermore, many of the enzymes involved in the processing of drugs also metabolize endogenous compounds. Their function is therefore needed to ensure homeostasis of the body. Until now the occurrence of drug metabolizing enzymes in the liver is not well defined, as most of the available observations describe exactly (quantitatively) only mRNA expression and in a less accurate way (semi-quantitatively) the enzymatic proteins. It does not constitute reliable background for an appropriate translation to their biological role, because not always correlation between the expression of mRNA and protein abundance occurs, and as mentioned above, inaccurate determination of the amount of the enzymes proteins contribute to the existing imperfections. Only few reports describe in a quantitative way the protein levels drug metabolizing enzymes in the healthy liver. In contrast, almost no quantitative description of drug metabolizing enzymes in the pathology of this organ is available. Thus, it is important to determine the abundance of drug metabolizing enzymes at the protein level by a quantitative method (liquid chromatography coupled to tandem mass spectrometry, LC-MS/MS), both in the healthy liver as well as in pathological conditions of the liver of a different pathophysiology, i.e. viral - hepatitis type C, cholestatic - primary sclerosing cholangitis, primary biliary cirrhosis and toxic - alcoholic liver disease. These findings will allow more accurate than the currently existing (based on semi-quantitative measurement methods of protein abundance) determination of drug metabolizing enzymes in liver pathologies of various etiology. Such a quantitative characteristics of drug metabolizing enzymes enable development of mathematical models for prediction of medications kinetics in the human body in pathological states in the liver.

Another aspect of the study is to search for mechanisms that affect gene expression and protein abundance of drug metabolizing enzymes in liver diseases (determination of miRNA profile and DNA methylation). Until now, there is no detailed information on the mechanisms involved in the regulation of drug metabolizing enzymes in the pathology of the liver. Their definition will contribute to better a understanding of pathological processes in the liver, which affect the bioavailability of drugs. Because of the involvement of the drug metabolizing enzymes in processing of many endogenous substances, the project will also provide information on the pathophysiological processes in the liver.