The role of brain glutamatergic system in the neuroendocrine regulation of cytochrome P450 expression and activity in the liver

The cytochromes P450 (CYP) are a superfamily of isoenzymes possessing the hemoprotein structure which play a role of terminal oxidase of the so called mixed function oxidase system. Most of CYP isoenzymes are present in the endoplasmic reticulum of hepatocytes where they play an important role in the oxidative metabolism of endogenous substances (e.g. steroids, arachidonic acid, neurotransmitters, vitamins) and exogenous compounds, including drugs and toxins. Knowledge of the regulation of cytochrome P450 in the liver by drugs and toxic substances at the level of the hepatocyte is already broad, however, physiological regulation of cytochrome P450 expression, especially the role of the nervous system in this regulation was only very recently noticed. So far, the studies concentrated mostly on the molecular regulation of cytochrome P450 expression at the level of the liver, taking into consideration the involvement of hormones and xenobiotics in the activation of membrane, cytoplasmic or nuclear receptors controlling cytochrome P450 gene expression. However, physiological regulation of cytochrome P450 expression, especially the role of the nervous system in this regulation was only very recently noticed. The studies of this problem, initiated in our department have indicated that the brain nervous system plays a significant role in regulation of cytochrome P450 expression in the liver.

The most important physiological regulators of the cytochrome P450 expression in the liver comprise such hormones as growth hormone, thyroid hormones, glucocorticoids, and sex hormones, which, *via* activation of the membrane, cytoplasmic or nuclear receptors, regulate the transcription of *CYP* genes. Secretion of the abovementioned hormones is controlled by the brain neuroendocrine system localized in the hypothalamus. Our earlier studies showed an important role of brain monoaminergic systems (dopaminergic, noradrenergic and serotonergic) in the neuroendocrine regulation of liver cytochrome P450 expression. But a possible role of amino acid neurotransmitters has not been studied in this respect, as yet. However, the problem is of high pharmacological and medical importance, since new psychotropic and neurological drugs acting on glutamate receptors are emerging. It is of great concern that apart from their targeted therapeutic effect, new drugs may seriously affect neuroendocrine regulation of different physiological processes including the expression of cytochrome P450.

The aim of our project is to study the effect of selected agonists/antagonists or modulators of glutamate receptors (potential drugs) on the neuroendocrine regulation of cytochrome P450 in the liver. We hypothesize that the selected compounds will induce significant changes in the functioning of the hypothalamic-pituitary-adrenal axis (HPA), the hypothalamic-pituitary-thyroidal axis (HPT) and the so-called hypothalamic-pituitary-liver axis (HPL, which affects growth hormone level) which, in turn, will lead to altered expression and activity of hormone-dependent cytochrome P450 isoforms in the liver. The studies will be carried out on male Wistar rats. The Selected specific agonists/antagonists or modulators of glutamatergic receptors will be administered intraperitoneally for a few days. Then, the following biochemical and molecular studies will be carried out: (1) determination of the hypothalamic, pituitary and respective peripheral gland hormones; (2) measurement of cytochrome P450 isoenzyme expression (protein and mRNA) in the liver; (3) measurement of the activities of cytochrome P450 isoenzymes in the liver.

The studies planned in this project will reveal new regulatory mechanisms of the liver cytochrome P450 involving glutamatergic system. The obtained results will not only broaden our basic knowledge on the contribution of individual glutamate receptors to the regulation of hormone secretion and, consequently, cytochrome P450 expression, but they may also have some pharmacological/medical significance. They should help to predict the effect of future drugs acting *via* glutamatergic system on hormonal system and cytochrome P450.