Session 9: Cytochrome P450-Expression Regulation in Nervous System

Lectures

L9.1

The regulation of liver cytochrome P450 by the brain nervous system

Władysława A. Daniel

Institute of Pharmacology, Polish Academy of Sciences, Smętna Street 12, 31-343 Kraków, Poland
Władysława Anna Daniel <nfdaniel@cyf-kr.edu.pl>

Cytochrome P450 is an important enzyme in psychopharmacology and therapy because it metabolizes psychotropic drugs and endogenous neuroactive substrates (neurosteroids, dopamine and serotonin precursors) in the liver and brain. Moreover, psychotropic drugs affect cytochrome P450, which may be partly connected with their pharmacological action in the brain.

Our recent studies indicate that the monoaminergic systems of the brain (dopaminergic, noradrenergic and serotonergic) can contribute to the physiological regulation of cytochrome P450 expression by engaging neuroendocrine mechanisms. These systems innervate the hypothalamic structures (paraventricular nuclei, arcuate nuclei, median eminence) connected with the regulation of pituitary hormone secretion, which leads to changes in the levels of blood hormones (growth hormone, corticosterone, thyroid hormones) regulating − *via* their respective membrane or cytosolic/nuclear receptors − liver cytochrome P450. In general, the brain catecholaminergic systems (dopaminergic and noradrenergic) produce stimulatory effect on rat CYP2C11, CYP3A and CYP2B, and an inhibitory effect on CYP1A. On the other hand, the brain serotonergic system seems to exert mostly opposite effect on cytochrome P450 compared to the catecholaminergic systems.

Hence the effect of neuroactive drugs on liver cytochrome P450 should be studied *in vivo* to comprise all possible mechanisms of enzyme regulation including those involving the brain neuroendocrine system.

L9.2

Consequences of muscle AMP deaminase deficiency caused by common nonsense mutation in *AMPD1* gene – a new look at the role of purine nucleotide cycle

Krzysztof Safranow

[1]Pomeranian Medical University in Szczecin, Department of Biochemistry and Medical Chemistry, Szczecin, Poland
Krzysztof Safranow <chrissaf@mp.pl>

AMP deaminase (AMPD) catalyzes AMP → IMP + NH_3 reaction as part of the purine nucleotide cycle. High AMPD activity in skeletal muscles is dominated by M isoenzyme encoded by *AMPD1* gene. For many years muscle AMPD deficiency has been associated with myopathy. In 1992 a nonsense C34T (Gln12Stop) *AMPD1* mutation was described as the molecular basis responsible for the vast majority of muscle AMPD deficiency cases. Currently, the homozygous defect (34TT genotype) is considered to be a harmless metabolic variant that can only worsen the clinical course of myopathy caused by other factors.

The C34T *AMPD1* mutation is an interesting model for the analysis of the role of AMP deamination and the purine nucleotide cycle in humans. Several reports have been published on the relationship of heterozygous genotype (34CT) with prolonged survival of patients with heart failure and significantly lower mortality from cardiovascular causes. However, later work, including author's own research, did not confirm the unambiguously beneficial effect of the mutation on the cardiovascular system.

There have been reports on the relationship of C34T mutation with various clinical, physiological and biochemical features in healthy subjects, including athletes, and in patients. In author's study the mutation was associated with a smaller waist circumference and a lower prevalence of diabetes in patients with coronary artery disease. Other studies have suggested the association of C34T mutation with reduced exercise capacity, limited response to physical training, and lower chance of achieving outstanding results in endurance and power sports. C34T mutation is considered a negative factor in multigene profiles estimating the predispositions for practicing sports. On the other hand, it is associated with a better vasodilator response to physical exercise and ischemia.

The suggested biochemical effects of the *AMPD1* C34T mutation that can prevent the development of obesity and diabetes are better glucose tolerance and increased insulin clearance. Effects on the immune system may be responsible for a better response to methotrexate therapy in the course of rheumatoid arthritis.

The proposed mechanisms of the *AMPD1* mutation influence include the role of increased concentration of AMPD substrate – AMP, which activates 5'AMP-activated protein kinase (AMPK) playing an important role in the regulation of carbohydrate and lipid metabolism. Another important factor may be increased concentration of adenosine produced by the action of 5'-nucleotidases on AMP, which exerts multidirectional effects on numerous organs and systems through A_1-A_3 receptors. In the light of these connections, AMP deaminase can be regarded as a potential target for drugs affecting various aspects of human metabolism.

Oral presentations

O9.1

Electrochemistry/liquid chromatography/ mass spectrometry for the simulation of *in vitro* metabolism of unsymmetrical bis-acridines with antitumor properties

Agnieszka Potęga, Aleksandra Robakowska, Magdalena Świeczkowska, Anna Mieszkowska

Gdańsk University of Technology, Faculty of Chemistry, Department of Pharmaceutical Technology and Biochemistry, Gabriela Narutowicza 11/12, Gdańsk 80-233, Poland
Agnieszka Potęga <agnieszka.potega@pg.edu.pl>

Metabolic studies are essential for predicting and understanding the fate of a drug in a human body. In this work, on-line electrochemistry/liquid chromatography/mass spectrometry (EC/LC/MS) coupling was employed to simulate the phase I metabolism of the selected unsymmetrical bis-acridines (UAs). UAs are a group of novel antitumor compounds that may be useful in the treatment of difficult to treat neoplasms, in particular pancreatic neoplasms. EC experiments were carried out under reductive and oxidative conditions in electrolytes of different composition and pH values. The reduction metabolites of nitro aromatic, nitroso, hydroxylamine, and amine species were produced. The major oxidative metabolic pathways identified for all studied compounds were due to the aromatic monohydroxylation of UA and *N*-demethylation in the 'linker' of two monomers. Importantly, UAs were stable in their dimeric forms during EC reactions. Moreover, the results of the electrochemical metabolism simulation were in good accordance with *in vitro* microsomal incubations, although each method provided unique products not identified with other approach. Future studies will extend the knowledge about the reactivity of nitroso species to biomolecules (e.g., glutathione) and other metabolites. The possibility to up-scale the electrochemical synthesis of certain metabolites in addition to the low matrix contribution compared to *in vitro* or *in vivo* biological models favors the use of EC in metabolic studies.