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Pharmacogenetics and the system of biotransformation of drugs

In this article the state and prospects of one of the modern directions of personalized medicine — pharmacogenetics are examined. General ideas about the role of biotransformation and metabolism of medicinal substances in pharmacogenetics were given, namely information on the polymorphism of genes involved in biotransformation of drugs and in the genetic control of their interaction, the description of the enzymes of the I and II phases of biotransformation of drugs.The first phase undergo oxidation, reduction and hydrolysis reactions in order to increase the polarity of the compound is described. In this phase, induction or inhibition by enzymes P450 is the main mechanism of drug interactions. The crystal structure of cytochrome P450 is studied. The main processes of the second phase of biotransformation are described: glucuronation, sulfation, conjugation with glycine, conjugation with glutathione, acetylation, methylation. Pathways of metabolism, enzymes involved in them, biotransformation phases are considered. The role of UDF-glucuronyltransferases in the transformation of drugs in the human body is shown. The classification of the superfamily of the UGT gene is described, the products of the members of this superfamily are described. The possibilities of genotyping using real-time PCR for the detection of individual single nucleotide polymorphisms, determination of the number of copies of the gene, pyrosequencing, mass spectrometry, matrix-activated laser desorption / ionization, and the use of microchips. The problems of drug use, such as drug toxicity, side effects, etc. are considered. Examples are given of the study of the effect of drugs on organisms in different countries. Such problems of genomic testing in our country as lack of funding, lack of clear cooperation between industrial and scientific circles, lack of specialists, creation of concrete and comprehensive.

Keywords: pharmacogenetics, cytochrome P450 isoenzymes, allele, UDF-glucuronyltransferase, polymorphic genes, genotypes, real-time PCR, LC marker, ferments of metabolism, gene expression.

A significant part of patients spend a large amount of money on drug treatment, and pharmacotherapy often does not justify the invested money. Most drugs do not satisfy all patients with their individual characteristics of susceptibility and tolerability of certain drugs. Patients face such problems as selecting the most suitable drugs for themselves, which will be more effective and less toxic. In the price plan, the analogues of medicines purchased are very expensive, and the free generics of well-known brands issued by the state do not bring the desired result. For realization of the state program on public health, 30 billion tenge was allocated from the state budget in 1995. By 2005, this amount increased by 185.5 billion, that is, by 155.5 billion tenge in absolute terms and 518.3 % in relative terms [1]. In 2010, budget purchases of medicines in Kazakhstan exceeded 77 billion KZT, this is already 44 % of the total domestic pharma market [2]. Also should be noted the fact that the state spends huge expenses on medicines and the fact that pharmapreparations do not justify the funds allocated for them, there is a question of getting out of this situation.

One of the ways to solve this problem is personalized medicine. Personalized medicine is a new direction in health care, which is characterized by an integrated, coordinated and individual approach to the treatment of the patient [3]. There is not only a difference in the sex or age characteristics among patients, it is also necessary to take into account the individual genetic characteristics of each patient [4, 5], so the approach to the use of medicines should be individual, and the use of technologies that allow personalizing pharmacotherapy will contribute it's optimization, making it as efficient and safe as possible. Moreover, it is economically advantageous, since it allows to minimize the acquisition of ineffective drugs and drugs with high toxicity and NLR.

The use of such technologies in clinical practice is the basis of personalized medicine. Based on the fact that the genetic characteristics of the patient more than 50 % can determine an inadequate pharmacological response, i.e. what we do not expect from drugs (ineffectiveness or development of NLR), personalization of drug use based on genetic research is the most promising direction.

Pharmacogenetic (Pgx) testing provides information on the therapeutic response to drug treatment or the patient's likelihood of having adverse drug reactions, which can potentially reveal the effectiveness or ineffectiveness of medications and find an individual approach to drug therapy [6]. The genetic differences of patients are estimated to be 20–95 % of the variation in individual responses to medications [7]. At present, the problem of improving the safety of the use of pharmacological drugs is very relevant. The effec-

tiveness of treatment, the presence or absence of side effects makes it possible to determine the extent of drug use by a particular population group [6].

Genetic features are polymorphic regions of genes, whose products, one way or another, participate in the realization of various pharmacokinetic and pharmacodynamic processes [8, 9].

At the present time, the role of genes that control the synthesis and operation of biotransformation enzymes is studied. These are cytochrome P-450 isozymes (CYP2D6, CYP2C9, CYP2C19, etc.), phase II biotransformation enzymes (N-acetyltransferase, glutathione-S-transferase) and Transporters of drugs (P-glycoprotein, carriers of organic anions and cations). Genes that encode the «target molecules» of the drug or, called the other way, functionally associated with these proteins (receptors, enzymes, ion channels). Also included are genes whose products are involved in various pathological processes (blood clotting factors, apolipoproteins, genes of the HLA system, etc.) against which appropriate pharmacotherapy is directed [8].

There are numerous reliable methods of genotyping, such as real-time PCR for individual single nucleotide polymorphisms (SNP) or for determining the number of copies of a gene, pyrosequencing, mass spectrometry, matrix-activated laser desorption/ionization (MALDI-TOF), as possibility of using microchips as well [10]. However, these studies underscore the complexities that arise at the level of the underlying mechanisms (zero alleles, partially functional alleles, substrate-dependent effects, bonded disequilibrium, etc.), as well as pharmacological and clinical levels (PD versus PK, adverse reactions, prodrugs, etc.). Drug toxicity and the result of treatment depends on the number of additional genetic and non-genetic factors, and not just on one genotype. Only in a few cases, with specific drugs and treatment regimens, can it be determined whether the patient will have a clearly predictable benefit from genotyping.

The need to implement the introduction of pharmacogenetic testing in clinical practice is due to its practical importance in the appointment and determination of drug dosing. However, the high expectations of the clinical use of pharmacogenetic testing remain largely unmet, and only a limited number of applications have actually entered the market and into clinical practice [11].

In this period there are a number of problems for the widespread clinical introduction of genomic medicine and pharmacogenetics [11, 12]. Thus, its potential impact on health and its socio-economic status remains uncertain.

There are such problems as lack of funding, lack of clear cooperation between industry and academia, lack of specialists, as well as the creation of a concrete and comprehensive regulatory and legal framework, lack of necessary technical equipment.

In addition, there are a number of other points that need to be considered when planning a pharmacogenetic test. So, to perform the test, the patient should take a single dose of LS_marker once, in addition, there is a chance of occurrence of unwanted reactions of the body. Difficulties and inconvenience for patients, risks with multiple blood sampling. The need to identify the concentration of LS_marker, as well as its metabolites in certain time intervals. When assessing the dynamics of biotransformation enzymes, one should take into account the fact that patients not only differ in genetic characteristics, but also have differences in age, sex and lifestyle (eating patterns, smoking, drinking alcohol, etc.). In addition, testing on large populations and sensitivity analysis for individual ethnic groups is difficult to achieve [13].

There is an alternative testing option, such as the identification of allelic variants of the biotransformation system genes and LS transports, in this case it is possible to predict the pharmacological response before taking the drug, since it is not required to receive LS_markers. Also, in this case, only a single intake of blood or other biological material (scraping from the inner surface of the cheek, hair) is required. In terms of the execution line, it is optimal, because, does not require a definition in in certain periods of time. For testing, equipment is required only for performing PCR, the cost of testing is minimal. Tests evaluate only the «genetic» component that affects the pharmacological response, and its results can be used to create the so-called pharmacogenetic passport of the patient. In addition, this test is acceptable for conducting large population studies [13].

First of all, it is necessary to study the peculiarities of the metabolism of drugs, whether it is an inducer or an inhaler. The substrate of which isoenzyme of the cytochrome P450 system it is, the features of the I-II phases of biotransformation

Phase I of the biotransformation reaction. System of cytochromes P450 participating in biotransformation of drugs. In the phase I of the biotransformation reaction, the functional groups of the preparation undergo oxidation, reduction and hydrolysis reactions in order to increase the polarity of the compound (Table 1). In the process of non-synthetic reactions, LSs turn into more polar and better water-soluble (hydro-

philic) compounds than the original substance. Although the first stage of the metabolism of drugs is carried out in most cases in tissues, the primary phase of metabolism occurs during hepatic circulation. Additional metabolism occurs in the gastrointestinal epithelium, kidneys, skin and lung tissue [8, 13].

Metabolism of most drugs in the first phase of biotransformation in the primary occurs in the liver with the participation of microsomal enzyme systems, the main one of which is the system of cytochromes P-450.

Cytochrome P450 (CYP) is a group of enzymes synthesized in the endoplasmic hepatic tissue network of heme-containing monooxygenases, which play a key role in xenobiotic detoxification, cellular metabolism and homeostasis. Isozymes of cytochrome P450 and its enzyme subfamily carry out oxidative reactions of xenobiotics and metabolism of intermediate products of drugs in the body. So, for example, isoenzymes of families CYP1, CYP2 and CYP3 bear joint responsibility for most of the phase I biotransformation reaction [13]. At present, 57 cytochrome P450 (CYP) genes and approximately the same number of pseudogenes that are grouped according to their sequence similarity into 18 families and 44 subfamilies have been identified in humans [14]. Eight human cytochrome P450 enzymes from five subfamilies (1A, 2B, 2C, 2D, 3A) are responsible for the vast majority of oxidative metabolism of drugs from the most important clinical drugs. Among the 200 drugs sold in the largest amount in the US, about 80 % is metabolized primarily by cytochrome P450 enzymes [10].

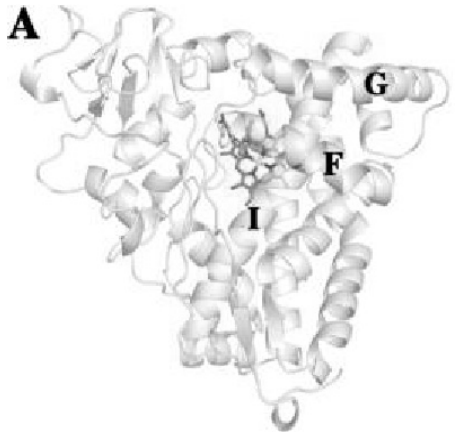


Figure 1. Crystal structure of cytochrome P450cam. A long spiral I permeates cytochrome through and helps to interact with the substrate and oxygen. Spirals F and G cause the mobility of cytochrome

The study of the crystal structures of cytochrome P450 isoenzymes (CYP) (Fig. 1) has opened the possibility of interpreting structural and functional features and other biologically important differences between cytochrome P450 (CYP) isoenzymes [15]. Prior to this time, there were significant inaccuracies in predicting amino acid sets that define substrate specificity for various cytochromes P450 (CYP) whose three-dimensional structures were not determined. However, now it has become easier to develop specific inhibitors or agonists related to cytochrome P450 isoenzymes (CYP).

The enzymes of cytochrome P450 are extremely versatile, they can catalyze numerous types of reaction. Oxygenations include the introduction of an O atom (from O_2) into a C–H bond, forming a hydroxylated metabolite, or a C=C double bond forming an epoxide. The hydroxylated metabolite may be stable or unstable. From the unstable hydroxylated metabolite of the group, spontaneously: an alkyl group, ammonia, a halogen atom, or a sulfur atom; such reactions are called oxidative dealkylation, oxidative deamination, oxidative dehalogenation, and oxidative desulfurization, respectively.

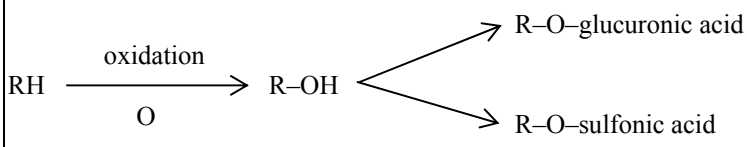
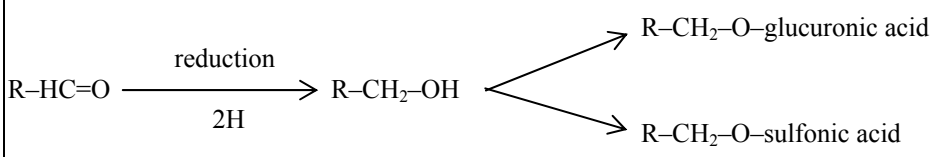
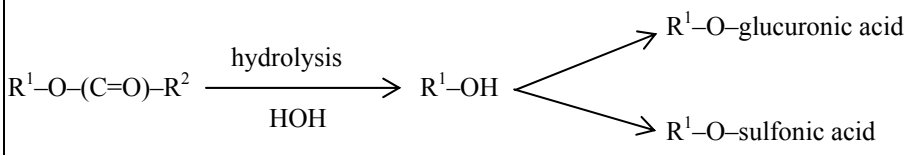
Changes in the initial physico-chemical properties of drugs are due to the addition or release of active functional groups: for example, hydroxyl (–OH), sulfhydryl (–SH), amino groups ($–NH_2$) [8].

These reactions have been characterized as mixed-functional oxidation, in which the enzymatic system catalyzes the consumption of one oxygen molecule / substrate molecule (RH); one atom of this oxygen molecule is inserted into the product (ROH), and the other is subjected to two reduction equivalents (Formula 1)

$$NADPH + RH + O_2 + H \rightarrow NADP + ROH + H_2O \quad (1)$$

Table 1

Reactions to which the functional groups of the drug undergo in phase I biotransformation

I Biotransformation reaction phase	1. Oxidation 2. Recovery 3. Hydrolysis
The chemical role of Phase I biotransformation	The conjugation reaction, in which a functional group is added to the molecule
Common examples	
	
	
	

The enzymes of cytochrome P450 also participate in the catalysis of dehydrogenation, i.e. Removal of 2 hydrogen atoms from the drug molecule (reactive hepatotoxic paracetamol metabolite is formed). Surprisingly, cytochrome P450 can also stimulate contraction, by transferring only one electron to the compound (for example, in a reductive dehalogenation reaction) or as many as 6 electrons to nitro groups, thus converting it to an amino group (a decrease in nitro).

Induction or inhibition by enzymes P450 is the main mechanism of drug interactions. Enzymes of cytochrome P450 (CYP) can transcriptively interact with various xenobiotics and endogenous substrates through the mechanism of receptor dependence. Because of the importance of cytochrome P450 in human physiology and in the metabolism of drugs, genetic variations and regulatory mechanisms of these enzymes have been extensively studied. Genetic polymorphisms have been identified in most cytochrome P450 genes [16], and many of these variants promote interpersonal differences in the expression gene or enzyme activity and, therefore, underpin the susceptibility or pharmacokinetics of drugs.

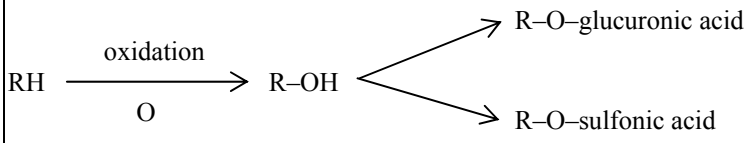
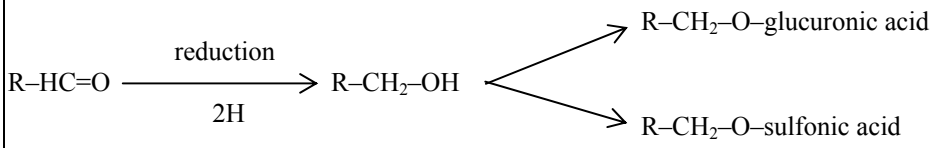
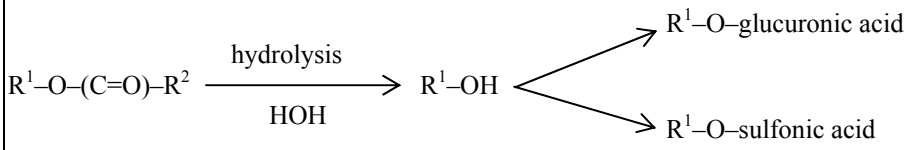
Phase II biotransformation reactions (also the 'conjugation reaction') usually serve as a detoxification step in the metabolism of drugs (Table 2) [8]. Although several enzymes of phase II of biotransformation are known, three basic enzymes of phase II biotransformation of medicinal substances were considered: UDP-glucuronyltransferase, N-acetyltransferase, glutathione S-transferase. The main attention is paid to the presence of various forms, on the tissue and cellular distribution, on the appropriate substrates, on genetic polymorphism and, finally, on the interspecies differences in these enzymes.

Table 2

Reactions to which the functional groups of the preparation under phase II biotransformation

Phase II biotransformation reactions (conjugation)	1. Glucuronation 2. Sulphation 3. Conjugation with glycine (Gly) 4. Conjugation from glutathione (GSH) 5. Acetylation 6. Methylation

Table 2 continuation

Chemical role of Phase II biotransformation	The organic acid (or acetyl or methyl group) is conjugated to the molecule in the pre-existing functional group or in the functional group obtained during the first phase of biotransformation
Common examples	
	
	
	

UDF-glucuronyltransferase — are among the key enzymes of metabolism of various exogenous, as well as endogenous compounds. A family of membrane-bound enzymes are mainly concentrated in the endoplasmic reticulum (ER) and nuclear envelope of hepatocytes. Most of the enzyme is oriented toward the ER side of the side, where the catalytic site is located. Each enzyme of the UDP-glucuronyltransferase includes an amino-terminal signal peptide that cleaves during the synthesis of the polypeptide chain and a region 17 of hydrophobic amino acids near the C-terminus that attaches the protein to the lipid bilayer (Fig. 2). Indeed, the C terminal of 20–30 amino acid residues is responsible for maintaining UDF-glucuronyl transferases (UGT) in ER. The conjugation of the reactions catalyzed by the superfamilies of these enzymes serve as the most important pathway detoxification for a wide range of drugs, biologically active chemicals, carcinogens and their oxidized metabolites and other various environmental chemicals in all vertebrates. In addition, UDP-glucuronyltransferase is involved in the regulation of several active endogenous compounds, such as bile acids or hydroxysteroids due to their inactivation by glucuronization [17]. In humans, almost 40–70 % of clinically used drugs undergo glucuronization [18].

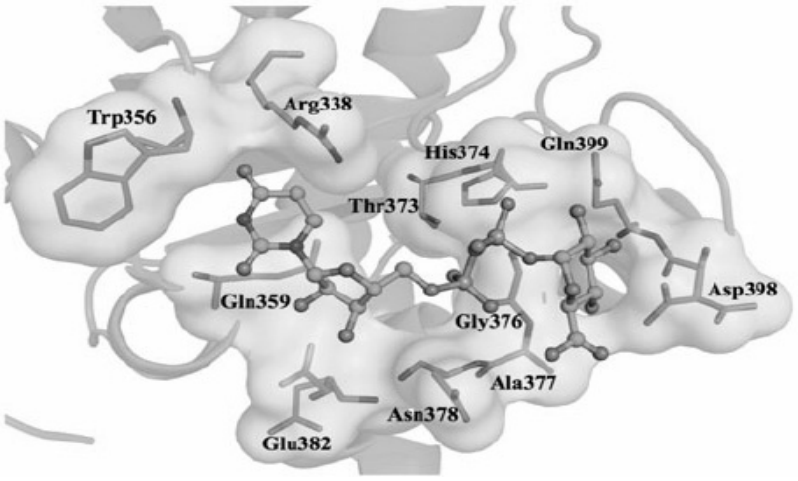


Figure 2. X-ray crystalline structure of human UGT2B7

Glucuronation is the main reaction to the II phase of drug metabolism, which is the conjugation of a substrate with UDP-glucuronic acid (Fig. 3). The reaction is catalyzed by the superfamily UDF-glucuronyl transferases (UGT), which consists of 2 families (UGT1 and UGT2) and more than 20 isozymes. Glucuronation leads to an increase in the polarity of chemical compounds, which facilitates their solubility in water and elimination from the body. In the organism of newborns, the activity of UDF-glucuronyltransferases is low, but by the 1–3 months of life it is the same as in adults.

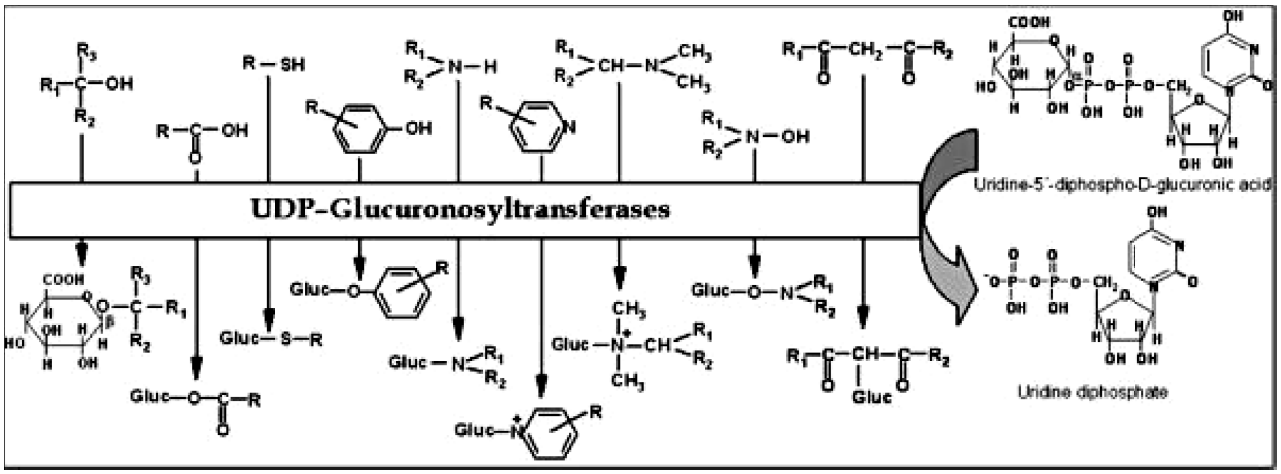


Figure 3. Formation of glucuronides. The chemical structures commonly subjected to glucuronization

For note, the superfamily of the mammalian UDP-glucuronyl transferase gene consists of 117 members. Four families of UDF-glucuronyl transferases were identified in humans: UGT1, UGT2 with the subfamily UGT2A and UGT2B, UGT3 and UGT8. Enzymes included in the subfamily UGT1 and UGT2 are responsible for the glucuronidation of exo and endogenous compounds, whereas members of the UGT3 and UGT8 subfamilies have their different functions [19]. Enzymes UDP-glucuronyltransferases each family has at least 40 % homology in the DNA sequence, whereas the members of the subfamilies of UDP-glucuronyltransferases exhibit at least 60 % identity in the DNA sequence [20]. Currently, 22 human protein described UGT: UGT1A1, UGT1A3, UGT1A4, UGT1A5, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2A1, UGT2A2, UGT2A3, UGT2B4, UGT2B7 (Fig.2), UGT2B10, UGT2B11, UGT2B15, UGT2B17, UGT2B28, UGT3A1, UGT3A2 and UGT8A1 [19, 21]. In general, human enzymes of UDF-glucuronyltransferases appear to be widely distributed across different tissues, although the liver is the main expression site for many enzymes. UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7 and UGT2B15 are major enzymes conjugated to xenobiotics by the liver, whereas UGT1A7, UGT1A8 and UGT1A10 are preferably extrahepatic forms UDP-glucuronyltransferases. In addition, glucuronidation activity was also found in other tissues, such as the kidneys [22], the brain [23], and the placenta [24].

First of all, it should be noted that most xenobiotics metabolized by UDF-glucuronyltransferases show different substrate specificities. UGT8A1 and UGT3A1, they have specific functions in the body. UGT8A1 is involved in the biosynthesis of glycosphingolipids, cerebrosides and sulphatides of nerve cells [25]. An enzyme UGT3A1 plays a role in the metabolism of ursodeoxycholic acid, used in the therapy of cholestasis or gallstones. Although many substrates (therapeutic agents, environmental chemicals) are glucuronidated by several UDP-glucuronyltransferases, several compounds show a relative specificity to individual enzymes. So bilirubin is exclusively metabolized by UGT1A1 [26]. In addition, the structure of the UGT1 gene is unique among related groups of genes involved in the metabolism of drug molecules. UGT1 isoforms are generated by alternative transcriptional splicing.

Genetic variability families UGT1 or UGT2 gene has also been proposed to modify the risk of cancer or as a result of declining hormones inactivation, such as estrogens, or due to the reduction of environmental carcinogen detoxification of the environment and their reactive metabolites

Families of enzymes glutathione transferase — play an important role in the metabolism of certain drugs, detoxification of environmental carcinogens and reactive intermediates, formed from various chemical enzymes, metabolizing xenobiotics. In addition, glutathione transferase formulates an important intracellular defense against oxidative stress, and also participates in the synthesis and metabolism of several arachidonic

acid derivatives and steroids. On the other hand, it has been proven that various chemicals are converted into potentially dangerous compounds by these enzymes [27].

Glutathione transferases are localized predominantly in the cytosol of human liver cells and constitute 2–4 % of the total amount of the cytosolic protein. The enzyme is effectively reduced hydrophobic hydroperoxides with a large amount of the molecule (linoleic and arachidonic hydroperoxide polyunsaturated fatty acids, phospholipids), as well as hydroperoxides mononucleotides and DNA, thereby participating in their repair.

At the present time, two different superfamilies of glutathione transferases (GST) have been described. The former includes soluble dimeric enzymes that are located mainly in the cytosol, but some members of this superfamily are also identified in mitochondria [28] and peroxisomes [29]. Superfamily soluble in humans glutathione further divided into eight separate classes: Alpha (A1-A4), Kappa (K1), Mu (M1-M5), Pi (P1), Sigma (S1), Theta (T1-T2), Zeta (Z1) and Omega (O1-O2) [30].

Various electrophilic compounds act as substrates for these groups of enzymes. These include a wide range of ketones, quinones, sulfoxides, esters, peroxides and ozonides. Chemotherapeutic agents (such as busulfan, cisplatin, ethacrynic acid, cyclophosphamide, thiotepa); Industrial chemicals, herbicides, pesticides (acrolein, lindane, malathion, tridifan) are detoxified by glutathione transferases [31].

The reaction catalyzed by the enzyme glutathione peroxidase is as follows:

$$2GSH + H_2O_2 \rightarrow GS–SG + 2H_2O \quad (2)$$

Where GSH is the reduced monomeric glutathione, and GS-SG is the glutathione disulphide. The glutathione reductase enzyme further reduces oxidized glutathione and completes the cycle (Formula 3)

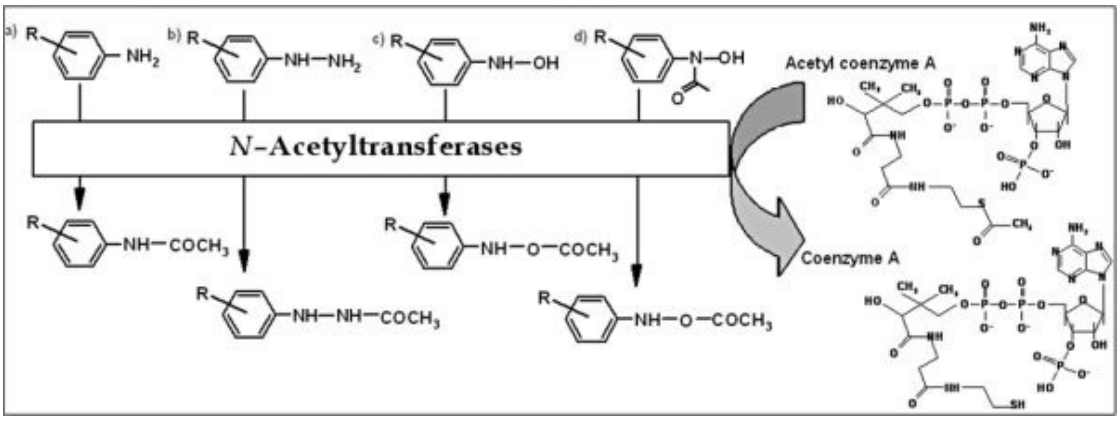
$$GS–SG + NADPH + H \rightarrow 2GSH + NAD \quad (3)$$

It was found that most members of superfamilies, such as glutathione transglutamine, are genetically polymorphic. It is assumed that several genetic variants of specific glutathione-transferases contribute to the development of some types of cancer or other diseases. In addition, the study of genetic polymorphisms of glutathione transferases, reveals their effect on the metabolism and distribution of various anticancer drugs [32]. For example, GSTP1 is responsible for the metabolism of alkylating agents, topoisomerase inhibitors, antimetabolites or tubulin inhibitors used to treat cancer. GSTP1*A allele is cytoprotective against the toxic effects of chemotherapeutic agents, whereas the functionally less competent GSTP1*B allele is believed to increase the toxicity of anti-cancer drugs in patients with this variant of the gene due to a decrease in the metabolic activity of the damaged enzyme. Cyclophosphamide is biotransformed with GSTA1. The defective GSTA1*B allele was associated with an increase in the survival of patients with breast cancer treated with cyclophosphamide [33]. Persons with a deficiency of functional GSTM1, GSTT1 and GSTP1 have a higher incidence of bladder, breast, colon, head, neck, and lung cancer. Genetically determined defects of these enzymes are also worthy of attention because of their partial responsibility for the increased risk of asthma, allergies, atherosclerosis and rheumatoid arthritis [31, 34].

N-acetyltransferase is an enzyme that plays an important role in the detoxification of a number of arylamine compounds (in particular, 2-aminofluoren, 4-aminobiphenyl and β-naphthylamine), which are strong mutagens and carcinogens; One of the two genes N-a. Human (NAT2) is located on the site of pter-q11 chromosome 8, and its coding region is deprived of introns. Enzymes of this group are three general reactions of acetylation, namely N-, O- and N,O-acetylation (Fig. 4). N-acetylation of aromatic amine is recognized as the main way of detoxification in the metabolism of arylamines in experimental animals and humans. In humans, the acetylation reactions are catalyzed by two isoenzymes of N-acetyltransferase (NAT), N-acetyltransferase 1 (NAT1) and 2 (NAT2). N-acetyltransferases are cytosolic enzymes found in many tissues of various species. NAT1 and NAT2 genes are located on chromosome 8 pter-q11 and have 87 % homology coding sequence [35]. NAT1 and NAT2 have a distinct substrate specificity and differ significantly in the distribution of organs and tissues. The NAT2 protein is present mainly in the liver [30] and in the intestine [36]. Human NAT1 expression was found in adult liver, bladder, digestive system, blood cells, placenta, skin, skeletal muscle, gum [37], breast tissue, prostate and lung by a variety of methods [38].

NAT1 has also been detected in cancer cells in which it can not only play a role in cancer development through enhanced mutagenesis, but it can also promote the resistance of some cancers to cytotoxic drugs [39]. N-acetyltransferases are involved in the metabolism of various compounds, people acetylation is the main pathway for biotransformation for many drugs, arylamine and hydrazine, as well as for a number of known carcinogens present in the diet, cigarette smoke, automobile exhaust and the environment as a whole.

Human NAT1 and human NAT2 have distinct but overlapping substrate profiles, and they also have specific substrates that can be used as probe probes for each particular isoenzyme. Substrates NAT1 include p-aminobenzoic acid, p-aminosalicylic acid, bacteriostatic antibiotics sulfamethoxazole and sulfonamide, 2-aminofluorene and caffeine [40].



(*a, b*) N-acetylation of arylamines and arylhydrazine; (*c*) O-acetylation of N-arylhydroxylamine; (*d*) N,O-acetyltransfer of N-hydroxamic acid

Figure 4. Reactions catalyzed by N-acetyltransferases

N-acetylation polymorphism is one of the oldest and most intensively studied pharmacogenetic traits and relates to hereditary differences in the acetylation of drugs and toxicants. Genetic polymorphism in NAT activity was first detected in tuberculosis patients who received isoniazid, which was metabolized mainly by N-acetylation. Polymorphism causes individual differences in the metabolic rate of this drug. People with a higher speed are called fast acetylators, and individuals with a lower speed are called slow acetylators. Fast acetylators were competent in the acetylation of isoniazid, but the drug was purified less efficiently in the slow acetylator group, which resulted in increased serum concentrations and resulted in adverse neurological side effects due to the accumulation of an unmetabolized drug [41]. In accordance with the toxicity of isoniazid in slow acetylators, an increase in the toxicity of other drugs in subjects with defective NAT2 alleles, such as lupus, in patients receiving hydralazine or procainamide [42], as well as hemolytic anemia and inflammatory bowel disease after sulfasalazine treatment has been observed [43]. The high frequency of NAT2 and NAT1 acetylation of polymorphism in the human population, together with the ubiquitous effects of aromatic and heterocyclic amines, suggest that NAT1 and NAT2 acetylatory genotypes are important modifiers of susceptibility to human cancer. Many studies have suggested a link between phenotypes of acetylation (in particular, arising from NAT2 genotypes) and the risk of developing various cancers, including colorectal cancer, liver, breast, prostate, head and neck [44] and other diseases such as birth defects [45] or neurodegenerative and autoimmune diseases [46].

Binding to the regulatory region of the biotransformation gene or the drug transporter, this mechanism inhibits enzymes of biotransformation of drugs under the influence of a large amount of the drug (cimetidine, fluoxetine, omeprazole, fluoroquinolones, macrolides, sulfonamides, etc.). Some drugs that have high affinity for certain isoenzymes of cytochrome P-450 (verapamil, nifedipine, isradipine, quinidine) inhibit the biotransformation of drugs with a lower affinity for these isoenzymes. Such mechanism is called a competitive metabolic interaction. Direct inactivation of cytochrome P-450 isoenzymes (gastoden). Oppression of cytochrome P-450 interaction with NADP-H-cytochrome P-450 reductase (fumarocoumarins of grapefruit and lime juice).

The decrease in the activity of enzymes of biotransformation of drugs under the action of appropriate inhibitors leads to an increase in the concentration in the blood plasma of these drugs (substrates for enzymes). At the same time, the half-life of medicinal substances is prolonged. All this causes the development of side effects. Some inhibitors affect several isoenzymes of biotransformation simultaneously. To inhibit several enzyme isoforms, higher concentrations of the inhibitor may be required. Thus, fluconazole (antifungal drug) at a dose of 100 mg per day inhibits the activity of the isoenzyme 2C9 cytochrome P-450. With an increase in the dose of this drug to 400 mg, inhibition of the activity of the isoenzyme 3A4 is also noted. In addition, the higher the dose of the inhibitor — the faster the development (and the higher) its effect. Inhibi-

tion generally develops faster than induction, usually it can be detected already after 24 hours from the time of administration of inhibitors. The rate of inhibition of enzyme activity is also influenced by the route of administration of the LS inhibitor: if the inhibitor is administered intravenously, the interaction process will occur faster.

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Дәрілік заттардың биоөзгеріс жүйесі және фармакогенетикасысы

Мақалада бүгінгі таңдағы жекешеленген медицинаның заманауи бағыты — фармакогенетиканың жағдайына және болашағына баға берілді. Фармакогенетикада дәрілік заттардың биоөзгерісі мен метаболизм рөлі туралы жалпы мәліметтер сарапталды, яғни, дәрілік заттардың биотрансформциясына қатысы бар және олардың әсеріне генетикалық бақылау жүргізетін гендердің полиморфизмі, биотрансформацияның I және II фазаларына қатысатын ферменттер туралы ақпарат берілді. Қосылыстың полярлығын ұлғайту үшін тотығу, тотықсыздандыру және гидролиз реакцияларына ұшырайтын биотрансфор-

мацияның бірінші фазасы сипатталды. Бұл кезеңде Р450 цитохром ферменттері әсерімен индукциялану немесе ингибирлену дәрілік заттардың әсер етуінің негізгі тетігі болып табылады. Р450 цитохром ферменттерінің кристалдық құрылымы сарапталды. Биотрансформацияның II фазалық кезеңінің негізгі процестері: глюкуронизациялану, сульфатациялану, глицинмен түйісу, глутатионмен түйісу, ацетилдену, метилдену. Биотрансформацияның II фазалық кезенінің метаболизм жолдары, УДФ-глюкуронилтрансфераза, N-ацетилтрансфераза, глутатион-S-трансфераза және тағы басқа ферменттер қаралды. Адам ағзасындағы дәрілік заттардың трансформациясындағы олардың рөлі туралы мәліметтер келтіріліп, тұқымдас ферменттердің жіктелуі, олардың өнімдері суреттелді. Генотиптеу үшін бірнуклеотидті полиморфизмдерді анықтау үшін арналған нақты уақыттағы ПТР, ген көшірмелерінің саның анықтау, пиросеквенирлеу, масс-спектрометрия, матрицалық-белсендірілген лазерлік десорбциялау/ионизациялау, сонымен қоса микрочиптерді пайдалану жолдары қарастырылды. Дәрілік заттардың қолдану кезіндегі дәрілік улағыштық, жанама және тағы басқа жағымсыз ықпалы жайлы мәселелер қозғалды. Әртүрлі мемлекеттердегі дәрілік заттардың ағзаға әсері туралы зерттеулер нәтижелері көрсетілді. Мемлекетіміздегі геномдық тестілеуді қаржыландырудың жоқтығы, өнеркәсіптік және ғылыми орталықтардың арасындағы ынтымақтастықтың болмауы, кәсіби мамандардың аздығы, нақты және бұл бағыттағы барлық өрістерді қамтитын құқықтық-нормативтік базаны құру мәселесі, сонымен қатар керекті техникалық қамтамасыздандырудың болмауына мән берілді.

Кілт сөздер: фармакогенетика, цитохром Р450 изоферментімен, аллель, полиморфты гендер, генотиптеу, ПТР нақты уақыттағы, ЛС маркер, УДФ-глюкуронилтрансфераза, метаболикалық ферменттер, геннің қозуы.

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Фармакогенетика и система биотрансформации лекарств

В статье рассмотрены состояние и перспективы одного из современных направлений персонализированной медицины — фармакогенетики. Даны общие представления о роли биотрансформации и метаболизма лекарственных веществ в фармакогенетике, а именно сведения о полиморфизме генов, вовлеченных в биотрансформацию лекарств и в генетический контроль их взаимодействия, описание ферментов I и II фаз биотрансформации лекарственных веществ. Описана первая фаза, на которой они подвергаются реакциям окисления, восстановления и гидролиза с целью увеличения полярности соединения. На этой фазе индукция или ингибирование ферментами Р450 является основным механизмом лекарственных взаимодействий. Изучена кристаллическая структура цитохрома Р450. Описаны основные процессы второй фазы биотрансформации: глюкуронирование, сульфатация, сопряжение с глицином, сопряжение с глутатионом, ацетилирование, метилирование. Рассмотрены пути метаболизма, ферменты, участвующие в них, фазы биотрансформации. Показана роль УДФ-глюкуронилтрансфераз в трансформации лекарственных средств в организме человека. Представлена классификация надсемейства гена UGT, описаны продукты членов этого надсемейства, Рассмотрены возможности генотипирования с использованием ПЦР в реальном времени для выявления индивидуальных однонуклеотидных полиморфизмов, определения числа копий гена, пиросеквенирование, масс-спектрометрия, матрично-активированная лазерная десорбция/ионизация, а также использование микрочипов. Рассмотрены такие проблемы применения лекарственных средств, как лекарственная токсичность, побочные эффекты и др. Приведены примеры изучения воздействия лекарственных средств на организмы в различных странах. Указаны такие проблемы геномного тестирования в нашей стране, как отсутствие финансирования, отсутствие четкого сотрудничества между промышленными и научными кругами, нехватка специалистов, создание конкретной и всеобъемлющей нормативно-правовой базы, отсутствие необходимого технического оснащения.

Ключевые слова: фармакогенетика, изофермент цитохром Р450, аллель, полиморфные гены, генотипирование, ПЦР в режиме реального времени, ЛС-маркер, УДФ-глюкуронилтрансфераза, ферменты метаболизма, экспрессия гена

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