

Phase II Drug Metabolism

Petra Jančová¹ and Michal Šiller²

¹*Department of Environmental Protection Engineering, Faculty of Technology,
Tomas Bata University, Zlin,*

²*Department of Pharmacology and Institute of Molecular and Translational Medicine,
Faculty of Medicine and Dentistry, Palacky University, Olomouc,
Czech Republic*

1. Introduction

All organisms are constantly and unavoidably exposed to xenobiotics including both man-made and natural chemicals such as drugs, plant alkaloids, microorganism toxins, pollutants, pesticides, and other industrial chemicals. Formally, biotransformation of xenobiotics as well as endogenous compounds is subdivided into phase I and phase II reactions. This chapter focuses on phase II biotransformation reactions (also called 'conjugation reactions') which generally serve as a detoxifying step in metabolism of drugs and other xenobiotics as well as endogenous substrates. On the other hand, these conjugations also play an essential role in the toxicity of many chemicals due to the metabolic formation of toxic metabolites such as reactive electrophiles. Gene polymorphism of biotransformation enzymes may often play a role in various pathophysiological processes. Conjugation reactions usually involve metabolite activation by a high-energy intermediate and have been classified into two general types: type I (e.g., glucuronidation and sulfonation), in which an activated conjugating agent combines with substrate to yield the conjugated product, and type II (e.g., amino acid conjugation), in which the substrate is activated and then combined with an amino acid to yield a conjugated product (Hodgson, 2004). In this chapter, we will concentrate on the most important conjugation reactions, namely glucuronide conjugation, sulfoconjugation, acetylation, amino acid conjugation, glutathione conjugation and methylation.

2. Phase II reactions

2.1 Glucuronidation

UDP-glucuronosyltransferases (UGTs) belong among the key enzymes of metabolism of various exogenous as well as endogenous compounds. Conjugation reactions catalyzed by the superfamily of these enzymes serve as the most important detoxification pathway for broad spectrum of drugs, dietary chemicals, carcinogens and their oxidized metabolites, and other various environmental chemicals in all vertebrates. Furthermore, UGTs are involved in the regulation of several active endogenous compounds such as bile acids or hydroxysteroids due to their inactivation via glucuronidation (Miners & McMackenzie, 1991; Kiang et al., 2005). In humans, almost 40-70% of clinically used drugs are subjected to

glucuronidation (Wells et al., 2004). In general, UGTs mediate the addition of UDP-hexose to nucleophilic atom (*O*-, *N*-, *S*- or *C*- atom) in the acceptor molecule (Mackenzie et al., 2008). The UDP-glucuronic acid is the most important co-substrate involved in the conjugation reactions (called glucuronidation) carried out by UGTs. Newly formed β -D-glucuronides exhibit increased water-solubility and are easily eliminated from the body in urine or bile. The scheme of typical glucuronidation reactions is shown in Figure 1. Glucuronidation *O*-linked moieties (acyl, phenolic, hydroxy) predominates the diversity in substrate recognition, and all of the UGTs are capable of forming *O*-linked glucuronides, albeit with different efficiencies and turn-over rates (Tukey & Strassburg, 2000). UGTs are membrane-bound enzymes similarly to cytochromes P450 with subcellular localization in the endoplasmic reticulum (ER). In contrast to cytochromes P450, the active site of these enzymes is embedded in the luminal part of ER.

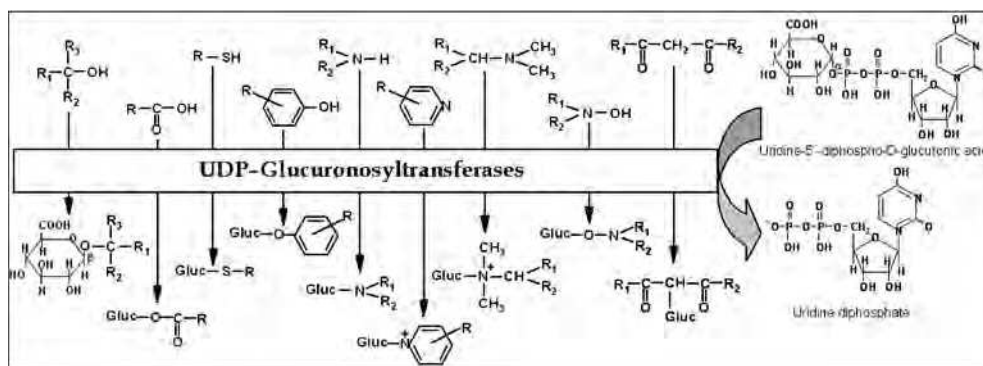


Fig. 1. Glucuronides formation. The summary of chemical structures commonly subjected to glucuronidation.

2.1.1 Human forms of UGTs and their tissue distribution

To date, the mammalian *UGT* gene superfamily comprises of 117 members. Four *UGT* families have been identified in humans: *UGT1*, *UGT2* involving *UGT2A* and *UGT2B* subfamily, *UGT3* and *UGT8*. Enzymes included in the *UGT1* and *UGT2* subfamily are responsible for the glucuronidation of exo- and endogenous compounds, whereas members of the *UGT3* and *UGT8* subfamilies have their distinct functions (See section *Substrates of UGTs, inhibition, induction*) (Mackenzie et al., 2008). The members of the *UGT1A* subfamily have been found to be identical in their terminal carboxyl 245 amino acids, which are encoded by exons 2-5. Only the uniqueness of first exon in the *UGT1A* subfamily genes differentiates one enzyme from each other. In contrast to the *UGT1A* subfamily, the members of the *UGT2* gene subfamily contain a different set of exons (Tukey & Strassburg, 2000). The *UGT* enzymes of each family share at least 40% homology in DNA sequence, whereas members of *UGT* subfamilies exert at least 60% identity in DNA sequence (Burchell et al., 1995). As of the time of writing, 22 human *UGT* proteins can be distinguished: *UGT1A1*, *UGT1A3*, *UGT1A4*, *UGT1A5*, *UGT1A6*, *UGT1A7*, *UGT1A8*, *UGT1A9*, *UGT1A10*, *UGT2A1*, *UGT2A2*, *UGT2A3*, *UGT2B4*, *UGT2B7*, *UGT2B10*, *UGT2B11*, *UGT2B15*, *UGT2B17*, *UGT2B28*, *UGT3A1*, *UGT3A2*, and *UGT8A1* (Mackenzie et al., 2008; Miners et al., 2006; Court et al., 2004; Patten, 2006; Sneitz et al., 2009). In general, human *UGT* enzymes

apparently exhibit a broad tissue distribution, although the liver is the major site of expression for many UGTs. The UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15 belong among the main liver xenobiotic-conjugating enzymes, whereas UGT1A7, UGT1A8, and UGT1A10 are predominantly extrahepatic UGT forms. Moreover, glucuronidation activity was also detected in other tissues such as kidney (Sutherland et al., 1993), brain (King et al., 1999), or placenta (Collier et al., 2002).

2.1.2 UGTs substrates. Inhibition and induction of UGTs

First of all, the fact that most xenobiotic metabolising UGTs show overlapping substrate specificities should be noted. Two UGTs, namely UGT8A1 and UGT3A1, stand apart from other UGT enzymes since they possess specific functions in the body. UGT8A1 takes part in the biosynthesis of glycosphingolipids, cerebroside, and sulfatides of nerve cells (Bosio et al., 1996). Recently, the UGT3A1 enzyme has been shown to have a certain role in the metabolism of ursodeoxycholic acid used in therapy of cholestasis or gallstones (Mackenzie et al., 2008). Although many substrates (therapeutic drugs, environmental chemicals) are glucuronidated by multiple UGTs, several compounds exhibit a relative specificity towards individual UGT enzymes. Bilirubin is exclusively metabolised by UGT1A1 (Wang et al., 2006). Conjugation reactions by the UGT2B7 enzyme constitute an important step in the metabolism of opioids (Coffman et al., 1998). Carboxylic acids including several non-steroidal anti-inflammatory agents are conjugated mainly by UGT1A3, UGT1A4, UGT1A9, and UGT2B7 (Tukey & Strassburg, 2000). Acetaminophen (paracetamol) is glucuronidated predominantly by UGTs of the UGT1A subfamily (UGT1A1, UGT1A6, and UGT1A9) (Court et al., 2001). Despite the fact that in most cases UGTs are responsible for *O*-glucuronidation of their substrates, members of the UGT1A subfamily have been found to catalyze *N*-glucuronidation of several amine-containing substrates (chlorpromazine, amitriptyline) (Tukey & Strassburg, 2000). The intestinal UGT1A8 and UGT1A10 enzymes were suggested to have a negative impact on the bioavailability of orally administered therapeutic drugs (Mizuma, 2009). For example, raloxifene, a selective estrogen receptor modulator used in therapy of osteoporosis, naturally has a low bioavailability and has also been shown to be extensively metabolised by UGT1A8 and UGT1A10 (Kemp et al., 2002). UGTs might also play a significant role in the inactivation of carcinogens from diet or cigarette smoke (Dellinger et al., 2006). Hanioka et al. (2008) proposed that the glucuronidation of bisphenol A (an environmental endocrine disruptor) by UGT2B15 serves as a major detoxification pathway of this molecule. UGTs are notably inhibited by various compounds. Analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), anxiolytics, anticonvulsants, or antiviral agents have been shown to have possible inhibitory effect on the enzymatic activities of various UGTs (thoroughly reviewed by Kiang et al., 2005). Recently, non-steroidal anti-inflammatory drugs have been shown to partially impair an equilibrium between biological functioning and degradation of aldosterone due to involvement of renal UGT2B7 in both the glucuronidation of aldosterone (deactivation) and the glucuronidation of NSAIDs (Knights et al., 2009). Similarly to other drug metabolising enzymes, UGTs are subject to induction by various xenobiotics or biologically active endogenous compounds (hormones) via nuclear receptors and transcription factors. For example, the aryl hydrocarbon receptor plays role in induction of UGT1A1 while the activation of pregnane X receptor and the constitutive androstane receptor leads to induction of UGT1A6 and UGT1A9 (Lin & Wong, 2002; Mackenzie et al., 2003; Xie et al., 2003). Several classes of drugs including analgesics, antivirals, or anticonvulsants are suspected to act as human UGTs inducers.

2.1.3 Genetic polymorphism in UGTs

Many human UGT enzymes were found to be genetically polymorphic. The mutations in *UGT1A1* gene result in several syndromes connected with decreased bilirubin detoxification capacity of UGT1A1. Kadakol et al. (2000) summed up data about more than 50 mutations of UGT1A1 causing Crigler–Najjar syndrome type I and type II. Patients suffering from type I, also called congenital familial nonhemolytic jaundice with kernicterus, completely lack the UGT1A1 enzymatic activity resulting in toxic effects of bilirubin on the central nervous system. The most common deficiency of UGT1A1 enzyme is Gilbert's syndrome. 2–12% of the population suffer from this benign disorder characterized by intermittent unconjugated hyperbilirubinemia. In most cases, this syndrome is caused by a mutation in the promotor region of *UGT1A1* gene (Monaghan et al., 1996). Increased toxicity of a pharmacologically active metabolite of irinotecan (SN-38) has been described in patients suffering from Gilbert's syndrome as UGT1A1 is the main enzyme responsible for the formation of the inactive SN-38 glucuronide (Wasserman et al., 1997). The genetic variability in the *UGT1* or *UGT2* gene families was also suggested to alter risk of cancer either as a result of decreased inactivation of hormones such as estrogens or due to reduced detoxification of environmental carcinogens and their reactive metabolites (Guillemette, 2003).

2.2 Sulfoconjugation

Sulfoconjugation (or sulfonation) constitutes an important pathway in the metabolism of numerous both exogenous and endogenous compounds. The sulfonation reaction was first recognized by Baumann in 1876. Baumann detected phenyl sulfate in the urine of a patient who had been administered phenol. The sulfonation reactions are mediated by a supergene family of enzymes called sulfotransferases (SULTs). In general, these enzymes catalyze the transfer of sulfonate (SO_3^-) from the universal sulfonate donor 3'-phosphoadenosine 5'-phosphosulfate (PAPS) to the hydroxyl or amino group of an acceptor molecule, Fig. 2. The incorrect term sulfation is sometimes used since sulfated products are formed in this type of reactions. PAPS is a universal donor of sulfonate moiety in sulfonation reactions and has been shown to be synthesized by almost all tissues in mammals from inorganic sulfate (Klaassen & Boles, 1997). Depletion of PAPS due to lack of inorganic sulfate or due to genetic defects of enzymes participating in PAPS synthesis may lead to reducing of sulfonation capacity which could affect the metabolism of xenobiotics or disrupt the equilibrium between synthesis and degradation of active endogenous compounds.

To date, two large groups of SULTs have been identified. The first group includes membrane-bound enzymes with no demonstrated xenobiotic-metabolising activity. These enzymes are localized in the Golgi apparatus and they are involved in metabolism of endogenous peptides, proteins, glycosaminoglycans, and lipids (Habuchi, 2000). Cytosolic SULTs constitute the second group of sulfotransferases and play a major role in conjugation of a broad spectrum of xenobiotics including environmental chemicals, natural compounds, drugs (Gamage et al., 2006) as well as endogenous compounds such as steroid hormones, iodothyronines, catecholamines, eicosanoids, retinol or vitamin D (Glatt & Meinel, 2004). Moreover, cytosolic SULTs are presumed to play a crucial role in the detoxification processes occurring in the developing human fetus since no UGTs transcripts have been detected in fetal liver at 20 weeks of gestation (Strassburg et al., 2002). Sulfonation is generally described as a detoxification pathway for many xenobiotics. Addition of the

sulfonate moiety to the molecule of a parent compound or most often to the molecule of its metabolite originating in the oxidative phase of drug metabolism leads to formation of a water-soluble compound which is then easily eliminated from the body. However, in several cases the sulfonation reaction can lead to formation of a more active metabolite compared to the parent compound as is the case for the hair follicle stimulant minoxidil (Buhl et al., 1990) or the diuretic agent triamterene (Mutschler et al., 1983). Furthermore, the role of sulfotransferases in the activation of various procarcinogens and promutagens was confirmed (Gilissen et al., 1994).

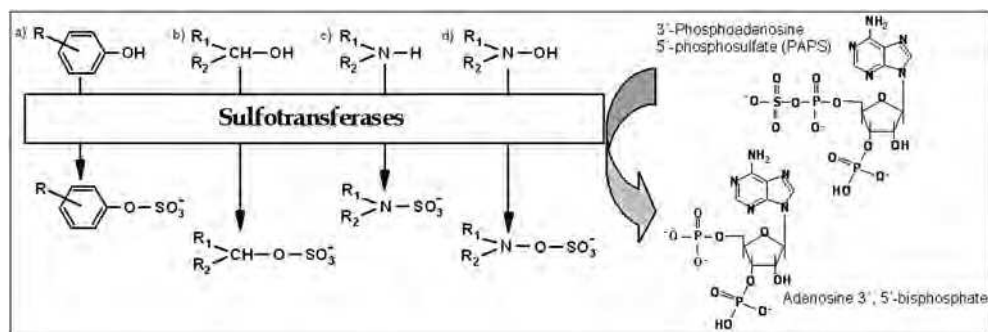


Fig. 2. The formation of sulfates ($R-O-SO_3^-$) and sulfamates ($R_1-NR_2-SO_3^-$). These reactions are catalyzed by 3'-phosphoadenosine 5'-phosphosulfate (PAPS)-dependent sulfotransferases.

2.2.1 Human forms of cytosolic SULTs and tissue distribution

In the following text we will focus only on cytosolic sulfotransferases, since this enzyme superfamily plays a key role in the biotransformation of multiple xenobiotics as well as endogenous substrates. Recently, a nomenclature system for the superfamily of cytosolic SULTs has been established analogously to those of other drug metabolising enzymes such as cytochromes P450 or UDP-glucuronosyltransferases (Blanchard et al., 2004). The superfamily of cytosolic sulfotransferases is subsequently divided into families and subfamilies according to the amino acid sequence identity among individual SULTs. In detail, members of one SULTs family share at least 45% amino acid sequence identity, whereas SULTs subfamily involves individual members with at least 60% identity. To date, four human SULT families, SULT1, SULT2, SULT4 and SULT6, have been identified. These SULT families include at least 13 different members. The SULT1 family comprises of 9 members divided into 4 subfamilies (1A1, 1A2, 1A3, 1A4, 1B1, 1C1, 1C2, 1C3 and 1E1). SULT2A (SULT2A1) and SULT2B (SULT2B1a and SULT2B1b) belong to SULT2 family. The SULT4A1 and SULT6B1 are the only members of the SULT4 and SULT6 family, respectively (Lindsay et al., 2008). Cytosolic sulfotransferases exert relatively broad tissue distribution. The members of SULT1A family were found in liver, brain, breast, intestine, jejunum, lung, adrenal gland, endometrium, placenta, kidney and in blood platelets. Figure 3 displays SULT expression "pies" of the most important human cytosolic transferases in human tissues. SULT1A1 is predominantly expressed in the liver (Hempel et al., 2007). In contrast to SULT1A1, the SULT1A3 enzyme was not detected in human adult liver. SULT1B1 has been found in liver, small intestine, colon, and leukocytes (Wang et al., 1998). Members of

SULT1C subfamily were identified in fetal human tissues such as liver (Hehonah et al., 1999) or lung and kidney (Sakakibara et al., 1998) as well as in adult human stomach (Her et al., 1997). The predominant expression of SULT1E1 was found in human liver and jejunum (Riches et al., 2009). Major sites of SULT2A1 expression are the liver, adrenal gland, ovary, and duodenum (Javitt et al., 2001). Members of SULT2B subfamily are localized in human prostate, placenta, adrenal gland, ovary, lung, kidney, and colon (Glatt & Meinel, 2004). Recently, an exclusive localization of human SULT4A1 in the brain was confirmed (Falany et al., 2000).

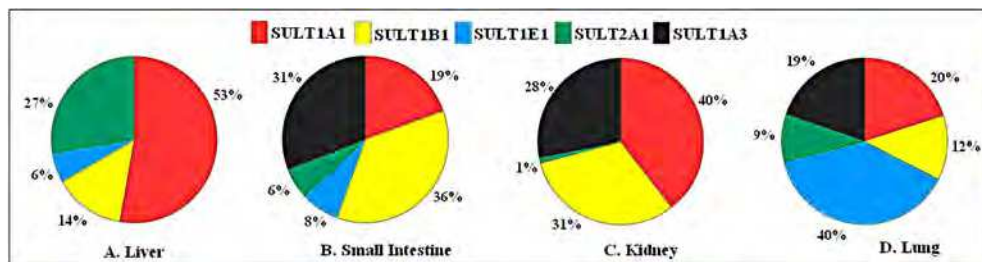


Fig. 3. The human SULT "pies". The mean expression values for each enzyme are displayed as percentages of the total sum of immunoquantified SULTs (maximum five enzymes) present in each tissue. Expression values are shown for liver (A), small intestine (B), kidney (C), and lung (D) (Riches et al., 2009).

2.2.2 Substrates of SULTs

SULT1A1 has been shown to be one of the most important sulfotransferases participating in metabolism of xenobiotics in humans. It has also been termed phenol sulfotransferase (P-PST) or thermostable phenol sulfotransferase (TS PST1). In general, SULT1A1 is responsible for sulfoconjugation of phenolic compounds such as monocyclic phenols, naphthols, benzylic alcohols, aromatic amines or hydroxylamines (Glatt & Meinel, 2004). Acetaminophen, minoxidil as well as dopamine or iodothyronines undergo sulfonation by SULT1A1. SULT1A1 also takes part in transformation of hydroxymethyl polycyclic aromatic hydrocarbons, *N*-hydroxyderivatives of arylamines, allylic alcohols and heterocyclic amines to their reactive intermediates which are able to bind to nucleophilic structures such as DNA and consequently act as mutagens and carcinogens (Glatt et al., 2001). SULT1A2 also plays an important role in the toxification of several aromatic hydroxylamines (Meinel et al., 2002). SULT1A3, formerly known as thermolabile phenol SULT (TL PST) or monoamine sulfotransferase, exhibits high affinity for catecholamines (dopamine) and contributes to the regulation of the rapidly fluctuating levels of neurotransmitters. The human SULT1B1 was isolated and described by Fujita et al. (1997) and was shown to be the most important sulfotransferase in thyroid hormone metabolism. SULT1E1 plays a key role in estrogen homeostasis. This enzyme conjugates 17β -estradiol and other estrogens in a step leading to their inactivation. Since 17β -estradiol and relative compounds regulate various processes occurring in humans, inactivation of these compounds by the SULT1E1 enzyme constitute an important step in the prevention and development of certain diseases. Down regulation or loss of SULT1E1 could be to a certain extent responsible for growth of tumor in hormone sensitive cancers such as breast or endometrial cancer (Cole et al., 2010). SULT2A and SULT2B subfamilies include the hydroxysteroid sulfotransferases with partially overlapping

substrate specificities. SULT2A1 is also termed as dehydroepiandrosterone sulfotransferase (DHEA ST) and conjugates various hydroxysteroids such as DHEA, androgens, bile acids and oestrone (Comer et al., 1993). Recently, a role of SULT2A1 in metabolism of quinolone drugs in humans was confirmed (Senggunprai et al., 2009). Clinically relevant substrates for other cytosolic sulfotransferases have not been identified yet.

2.2.3 Genetic polymorphisms in SULTs

Genetic polymorphism was detected in many SULT forms such as the SULT1A1, SULT1A3, SULT1C2, SULT2A1, SULT2A3 and SULT2B1 enzyme (Lindsay et al., 2008). Single nucleotide polymorphism in the *SULT1A1* gene leading to an Arg₂₁₃ → His amino acid substitution is relatively frequent in the Caucasian population (25.4–36.5%) (Glatt & Meinel, 2004). This mutation results in a variation of SULT1A1 thermal stability and enzymatic activity. Several authors have claimed that SULT1A1 polymorphism might play a role in the pathophysiology of lung cancer (Arslan et al., 2009), urothelial carcinoma (Huang, 2009), and meningioma brain tumors (Bardakci, 2008).

2.3 Glutathione S-conjugation

Since the first detection of glutathione transferase activity in rat liver cytosol by Booth in the early 1960s, the family of glutathione transferases (synonymously glutathione S-transferases; GSTs) has been studied in detail. Undoubtedly, the members of glutathione transferase family play an important role in metabolism of certain therapeutics, detoxification of environmental carcinogens and reactive intermediates formed from various chemicals by other xenobiotic-metabolising enzymes. Furthermore, GSTs constitute an important intracellular defence against oxidative stress and they appear to be involved in synthesis and metabolism of several derivatives of arachidonic acid and steroids (van Bladeren, 2000). On the other hand, various chemicals have been shown to be activated into potentially dangerous compounds by these enzymes (Sherratt et al., 1997). In general, these enzymes catalyze a nucleophilic attack of reduced glutathione on lipophilic compounds containing an electrophilic atom (C-, N- or S-). In addition to nucleophilic substitutions, these transferases also account for Michael additions, isomerations, and hydroxyperoxide reductions. In most cases, more polar glutathione conjugates are eliminated into the bile or are subsequently subjected to other metabolic steps eventually leading to formation of mercapturic acids. Figure 4 shows the sequential steps in the synthesis of mercapturic acids. Mercapturic acids are excreted from the body in urine (Commandeur et al., 1995). For instance, industrial chemicals such as acrylamide or trichloroethylene are detoxified via mercapturic acids (Boettcher et al., 2005; Popp et al., 1994).

2.3.1 Differentiation of GSTs, their cellular localization and tissue distribution

Up to now, two different superfamilies of GSTs have been described. The first one includes soluble dimeric enzymes localized mainly in cytosole but certain members of this superfamily have been also identified in mitochondria (Robinson et al., 2004) or in peroxisomes (Morel et al., 2004). The superfamily of human soluble GSTs is 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) (Hayes et al., 2005). Microsomal GSTs designated as the membrane associated proteins in eicosanoid and glutathione metabolism

(MAPEG) constitute the second family of human GSTs. The human MAPEG superfamily includes six members: 5-lipoxygenase activating protein (FLAP), leukotriene C₄ synthase (both involved in leukotriene synthesis), MGST1, MGST2, MGST3 (GSTs as well as glutathione dependent peroxidases) and prostaglandin E synthase (PGES) (Bresell et al., 2005). Both the soluble GSTs and MAPEG exhibit a broad tissue distribution; being found in liver, kidney, brain, lung, heart, pancreas, small intestine, prostate, spleen, and skeletal muscles (Hayes & Strange, 2000).

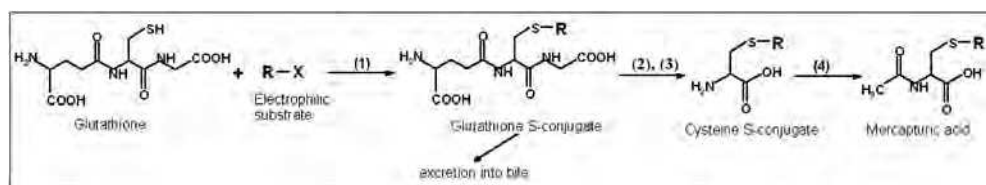


Fig. 4. Formation of mercapturic acid. Glutathione S-transferase (1) catalyzes the conjugation between glutathione and various endogenous or xenobiotic electrophilic compounds. Subsequently, the resulting glutathione S-conjugate is broken down to a cysteine S-conjugate by γ -glutamyltranspeptidase (2) and dipeptidases (3). Finally, cysteine S-conjugate N-acetyltransferase (4) catalyses formation of mercapturic acid.

2.3.2 Substrates of human GSTs

Various electrophilic compounds act as substrates for GSTs. They include a broad spectrum of ketones, quinones, sulfoxides, esters, peroxides, and ozonides (van Bladeren et al., 2000). Chemotherapeutics (such as busulfan, cis-platin, ethacrynic acid, cyclophosphamide, thiotepea); industrial chemicals, herbicides, pesticides (acrolein, lindane, malathion, tridiphane) are detoxified by GSTs (Hayes et al., 2005). Epoxides and other reactive intermediates formed from environmental procarcinogens mostly as a result of metabolism by cytochromes P450 (aflatoxin B₁, polycyclic aromatic hydrocarbons, styrene, benzopyrene, heterocyclic amines) also undergo detoxification by soluble GSTs. Besides their enzymatic activity, cytosolic GSTs (such as class Alpha) exhibit an ability to bind various hydrophobic ligands (xenobiotics as well as hormones) and thus contribute to their intracellular transport and disposition. GSTs play an essential role in the fight against products of oxidative stress which unavoidably damage cell membrane lipids, DNA, or proteins. Reactive intermediates resulting from lipid peroxidation (4-hydroxynonenal), nucleotide peroxidation (adenine propenal) or catecholamine peroxidation (aminochrome, dopachrome, adrenochrome) are particularly inactivated by GSTs (Dagnino-Subiabre et al., 2000). Several specific substrates for GSTs have been identified. For instance, ethacrynic acid has been found to be predominantly metabolised by GSTP1, whereas trans-stilbene oxide is a specific substrate for GSTM1 (van Bladeren, 2000). The GSTT1 enzyme is responsible for conjugation of halogenated organic compounds such as dichloromethane or ethylene-dibromide (Landi, 2000). This step leads to activation of these compounds to their reactive electrophilic metabolites with potential mutagenic and cancerogenic effect. Ethylene-dibromide, a gasoline additive and a fumigant, is presumed to be potential human carcinogen because it is transformed by GSTs to DNA-reacting episulfonium ion (van Bladeren, 2000). The glucocorticoid response element and the xenobiotic response element activated by glucocorticoids and planar aromatic hydrocarbons respectively might play a role in the induction of expression of GSTs (Talalay et al., 1988).

2.3.3 Genetic polymorphism in GSTs

Most members of both glutathione transferase superfamilies have been found to be genetically polymorphic. Several genetic variants of particular GSTs are supposed to contribute to the development of certain cancers or other diseases. Furthermore, genetic polymorphism in GSTs is presumed to influence metabolism and disposition of various anticancerogenic drugs (Crettol et al., 2010). *GSTP1* is responsible for metabolism of alkylating agents, topoisomerase inhibitors, antimetabolites, or tubulin inhibitors used in treatment of cancer. The common allele *GSTP1**A is cytoprotective against the toxic effects of chemotherapeutics, whereas the functionally less competent allele *GSTP1**B is thought to increase the toxicity of anticancerogenic drugs in patients with this gene variant due to decreased metabolic activity of impaired enzyme. Cyclophosphamide is biotransformed by *GSTA1*. Defective *GSTA1**B allele was associated with increased survival in breast cancer patients treated with cyclophosphamide (Sweeney et al., 2003). On the other hand, several drugs activated by GSTs require a well-functioning enzyme. Patients with the active *GSTM1* gene treated for acute myeloid leukemia with doxorubicin had a superior survival rate compared to patients with at least one null allele (Autrup et al., 2002). Individuals with lacking functional *GSTM1*, *GSTT1*, and *GSTP1* have been shown to have a higher incidence of bladder, breast, colorectal, head/neck, and lung cancer. Genetically-based defects of these enzymes are also noteworthy because of their partial responsibility for increased risk of asthma, allergies, atherosclerosis, and rheumatoid arthritis (van Bladeren, 2000; Hayes et al., 2005).

2.4 Acetylation

Compared to sulfonations and glucuronidations, acetylations are modest in terms of the number and variety of substrates, but remain significant in a toxicological perspective. Drugs and other foreign compounds that are acetylated in intact animals are either aromatic amines or hydrazines, which are converted to aromatic amides and aromatic hydrazides (Parkinson, 2001). Acetylation reactions are characterized by the transfer of an acetyl moiety, the donor generally being acetyl coenzyme A, while the accepting chemical group is a primary amino function. As far as xenobiotic metabolism is concerned, three general reactions of acetylation have been documented, namely *N*- (Fig. 5a, b), *O*- (Fig. 5c), and *N,O*-acetylations (Fig. 5d). *N*-acetylation of aromatic amine is recognized as a major detoxification pathway in arylamine metabolism in experimental animals and humans (Hein et al., 2000). However, *O*- and *N,O*-acetylations occur in alternative metabolic pathways following activation by *N*-hydroxylation. The resulting *N*-acetoxyarylamines are highly unstable, spontaneously forming arylnitrenium ions that bind to DNA (Bland & Kadlubar, 1985) and ultimately lead to mutagenesis and carcinogenesis (Kerdar et al., 1993).

2.4.1 *N*-Acetyltransferases

In humans, acetylation reactions are catalyzed by two *N*-acetyltransferase isoenzymes (NATs), *N*-acetyltransferase 1 (NAT1) and 2 (NAT2). NATs are cytosolic enzymes found in many tissues of various species. The human *NAT1* and *NAT2* genes are located on chromosome 8 pter-q11, and share 87% coding sequence homology (Blum et al., 1990). *NAT1* and *NAT2* have distinct substrate specificities and differ markedly in terms of organ and tissue distribution. *NAT2* protein is present mainly in the liver (Grant et al., 1990) and intestine (Hickman et al., 1998). *NAT1* appears to be ubiquitous. Expression of human *NAT1*

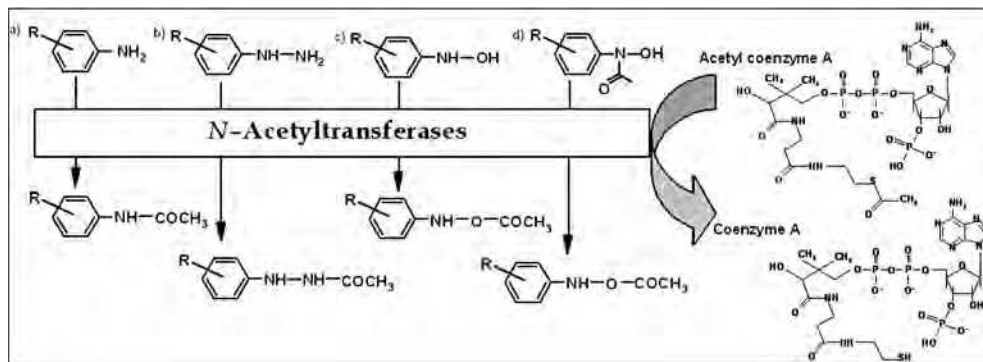


Fig. 5. Reactions catalysed by *N*-acetyltransferases. (a,b) *N*-acetylation of arylamine and arylhydrazine, (c) *O*-acetylation of *N*-arylhydroxylamine, (d) *N*, *O*-acetyltransfer of an *N*-hydroxamic acid. These reactions use acetyl-coenzyme A as acetyl donor.

has been detected in adult liver, bladder, digestive system, blood cells, placenta, skin, skeletal muscles, gingiva (Dupret & Lima, 2005), mammary tissue, prostate, and lung by a number of methods (Sim et al., 2008). A notable difference between the two isoenzymes is the presence of NAT1 activity in fetal and neonatal tissue, such as lungs, kidneys, and adrenal glands (Pacifci et al., 1986). By contrast, NAT2 is not evident until about 12 months after birth (Pariente-Khayat et al., 1991). NAT1 has also been detected in cancer cells, in which it may not only play a role in the development of cancers through enhanced mutagenesis but may also contribute to the resistance of some cancers to cytotoxic drugs (Adam et al., 2003). NATs are involved in the metabolism of a variety of different compounds to which we are exposed on a daily basis. In humans, acetylation is a major route of biotransformation for many arylamine and hydrazine drugs, as well as for a number of known carcinogens present in diet, cigarette smoke, car exhaust fumes, and environment in general. Human NAT1 and human NAT2 have distinct but overlapping substrate profiles and also have specific substrates which can be used as "probe" substrates for each particular isoenzyme. Substrates of NAT1 include *p*-aminobenzoic acid, *p*-aminosalicylic acid, the bacteriostatic antibiotics sulfamethoxazole and sulfanilamide, 2-aminofluorene and caffeine (Ginsberg et al., 2009). Moreover, it has been proposed by Minchin that human NAT1 plays a role in folate metabolism through the acetylation of the folate metabolite *p*-aminobenzoylglutamate (Minchin, 1995). Human NAT2 is a xenobiotic-metabolising enzyme that provides a major route of detoxification of drugs such as isoniazid (an anti-tuberculosic drug), hydralazine and endralazine (anti-hypertensive drugs), a number of sulphonamides (anti-bacterial drugs) (Kawamura et al., 2005), procainamide (anti-arrhythmic drug), aminoglutethimide (an inhibitor of adrenocortical steroid synthesis), nitrazepam (a benzodiazepine) and the anti-inflammatory drug dapsone (Ginsberg et al., 2009; Butcher et al., 2002). Both NAT1 and NAT2 are polymorphic enzymes, with 28 NAT1 and 64 NAT2 alleles having been identified to date (see <http://louisville.edu/medschool/pharmacology/NAT.html> for details of alleles; last update May 24, 2011). *N*-acetylation polymorphism represents one of the oldest and most intensively studied pharmacogenetic traits and refers to hereditary differences concerning the acetylation of drugs and toxicants. The genetic polymorphism in NAT activity was first

recognised in tuberculosis patients treated with isoniazid, which is metabolised principally by *N*-acetylation. The polymorphism causes individual differences in the rate of metabolism of this drug. Individuals with a faster rate are called rapid acetylators and individuals with a slower rate are called slow acetylators. Rapid acetylators were competent in isoniazid acetylation but the drug was cleared less efficiently in the slow acetylator group, which resulted in elevated serum concentration and led to adverse neurologic side effects due to an accumulation of unmetabolized drug (Brockton et al., 2000). Consistent with the toxicity of isoniazid in slow acetylators, there is an increased incidence of other drug toxicities in subjects carrying defective *NAT2* alleles, such as lupus erythematosus in patients treated with hydralazine or procainamide (Sim et al., 1988), and haemolytic anemia and inflammatory bowel disease after treatment with sulfasalazine (Chen et al., 2007). The high frequency of the *NAT2* and also *NAT1* acetylation polymorphism in human population together with ubiquitous exposure to aromatic and heterocyclic amines suggest that *NAT1* and *NAT2* acetylator genotypes are important modifiers of human cancer susceptibility. Many studies suggested a relationship between acetylation phenotypes (in particular, arising from *NAT2* genotypes) and the risk of various cancer including colorectal, liver, breast, prostate, head and neck (Agúndez, 2008) and other disease conditions such as birth defects (Lammer et al., 2004) or neurodegenerative and autoimmune diseases (Ladero, 2008).

2.5 Methylation

Methylation is a common but generally minor pathway of xenobiotic biotransformation. Unlike most other conjugative reactions, methylation often does not dramatically alter the solubility of substrates and results either in inactive or active compounds. Methylation reactions are primarily involved in the metabolism of small endogenous compounds such as neurotransmitters but also play a role in the metabolism of macromolecules for example nucleic acids and in the biotransformation of certain drugs. A large number of both endogenous and exogenous compounds can undergo *N*- (Fig. 6a), *O*- (Fig. 6b), *S*- (Fig. 6c) and arsenic-methylation during their metabolism (Feng et al., 2010). The co-factor required to form methyl conjugates is *S*-adenosylmethionine (SAM), which is primarily formed by the condensation of ATP and *L*-methionine.

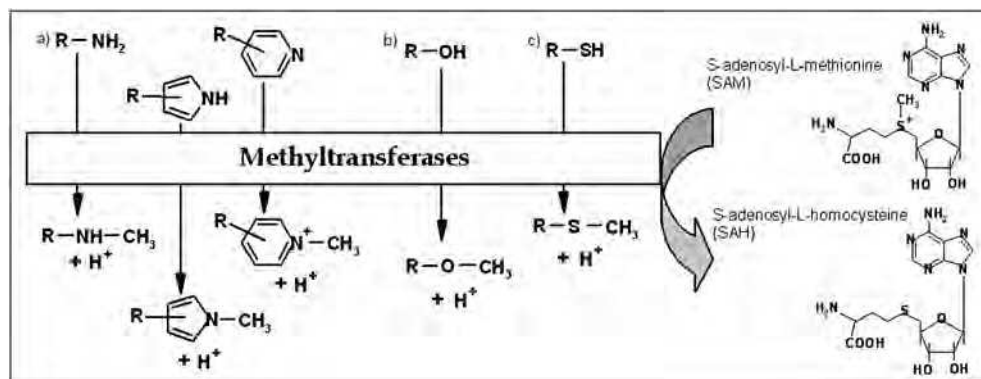


Fig. 6. Methylation reactions catalyzed by methyltransferases.

2.5.1 N-methylation

Several *N*-methyltransferases have been described in humans and other mammals; including *indolethylamine N-methyltransferase (INMT)*, which catalyzes the *N*-methylation of tryptamine and structurally related compounds. The INMT exhibits wide tissue distribution. Human INMT was expressed in the lung, thyroid, adrenal gland, heart, and muscle but not in the brain (Thompson et al., 1999). Since INMT is predominantly present in peripheral tissues, its main physiological function is presumably non-neural. *Nicotinamide N-methyltransferase (NNMT)* is a SAM-dependent cytosolic enzyme that catalyzes the *N*-methylation of nicotinamide, pyridines, and other structural analogues. NNMT is predominantly expressed in the liver; expression has been also reported in other tissues such as the kidney, lung, placenta, and heart (Zhang et al., 2010). Several *N*-methylated pyridines are well-established dopaminergic toxins and the NNMT can convert pyridines into toxic compounds (such as 4-phenylpyridine into *N*-methyl-4-phenylpyridinium ion [MPP⁺]). NNMT has been shown to be present in the human brain, a necessity for neurotoxicity, because charged compounds cannot cross the blood-brain barrier (Williams & Ramsden, 2005). NNMT was one of the potential tumor biomarkers identified in a wide range of tumors such as thyroid, gastric, colorectal, renal, and lung cancer (Zhang et al., 2010). *Histamine N-methyltransferase (HNMT)*, the second most important histamine inactivating enzyme, is a cytosolic enzyme specifically methylating the imidazole ring of histamine and closely related compounds in the intracellular space of cells. Levels of HNMT activity in humans are regulated genetically. HNMT is widely expressed in human tissues; the greatest expression is in the liver and kidney, but also in the spleen, colon, prostate, ovary, brain, bronchi, and trachea (Maintz & Novak, 2007). Common genetic polymorphisms for HNMT might be related to a possible role for individual variation in histamine metabolism in the pathophysiology of diseases such as allergy, asthma, peptic ulcer disease, and some neuropsychiatric illnesses (Preuss et al., 1998). *Phenylethanolamine N-methyltransferase (PNMT)* plays a role in neuroendocrine and blood pressure regulation in the central nervous system. PNMT, the terminal enzyme of the catecholamine biosynthesis pathway, catalyzes the *N*-methylation of the neurotransmitter norepinephrine to form epinephrine (Ji et al., 2005). PNMT is a cytosolic enzyme that is present in many tissues throughout the body, with particularly high concentration in the adrenal medulla, adrenergic neurons in the amygdala and retina and the left atrium of the heart (Haavik et al., 2008). Its activity increases after stress in response to glucocorticoids and neuronal stimulation (Saito et al., 2001). Several studies have suggested that two common *PNMT* promoter single nucleotide polymorphisms might be associated with risk of diseases such as essential hypertension, early-onset Alzheimer's disease, or multiple sclerosis (Ji et al., 2008). *Phosphatidylethanolamine N-methyltransferase (PEMT)* converts phosphatidylethanolamine to phosphatidylcholine in mammalian liver. Phosphatidylcholine is nutrient critical to many cellular processes such as phospholipid biosynthesis, lipid-cholesterol transport, or transmembrane signaling. The human *PEMT* gene encodes for two isoforms of the enzyme, namely *PEMT1*, which is localized in the endoplasmic reticulum and generating most of the *PEMT* activity, and *PEMT2*, a liver specific isoform exclusively localized in mitochondria-associated membranes (Tessitore et al., 2003).

2.5.2 O-methylation

The process of *O*-methylation of phenols and catechols is catalyzed by two different enzymes known as phenol *O*-methyltransferase and catechol *O*-methyltransferase. *Phenol*

O-methyltransferase (POMT) is an enzyme that transfers the methyl group of SAM to phenol to form anisole. POMT is localized in the microsomes of the liver and lungs of mammals but is also present in other tissues. *Catechol O*-methyltransferase (COMT) is a magnesium-dependent enzyme which was first described by Axelrod in 1957. It is an enzyme that plays a key role in the modulation of catechol-dependent functions such as cognition, cardiovascular function, and pain processing. COMT is involved in the inactivation of catecholamine neurotransmitters such as epinephrine, norepinephrine, and dopamine, but also catecholestrogens and catechol drugs such as the anti-Parkinson's disease agent L-DOPA and the anti-hypertensive methyl dopa (Weinshilboum et al., 1999). Two forms of human COMT have been identified, a cytoplasmic soluble form (S-COMT) and a membrane-bound form (MB-COMT) located in the cytosolic side of the rough endoplasmic reticulum. The S-COMT is predominantly expressed in the human liver, intestine and kidney (Taskinen et al., 2003), whereas the membrane-bound form is more highly expressed in all regions of the human central nervous system (Tunbridge et al., 2006). A common functional polymorphism at codons 108 and 158 in the genes coding for S-COMT and MB-COMT (COMT Val 108/158 Met), respectively, has been examined in relationship to a number of neurological disorders involving the noradrenergic or dopaminergic systems, such as schizophrenia (Park et al., 2002) or Parkinson's disease (Kunugi et al., 1997). It has also been suggested that a common functional genetic polymorphism in the COMT gene may contribute to the etiology of alcoholism (Wang et al., 2001).

2.5.3 S-methylation

Thiol methylation is important in the metabolism of many sulfhydryl drugs. Human tissues contain two separate genetically regulated enzymes that can catalyze thiol S-methylation. *Thiol methyltransferase* (TMT) is a membrane-bound enzyme that preferentially catalyzes the S-methylation of aliphatic sulfhydryl compounds such as captopril and D-penicillamine, whereas *thiopurine S-methyltransferase* (TPMT) is a cytoplasmic enzyme that preferentially catalyzes the S-methylation of aromatic and heterocyclic sulfhydryl compounds including anticancer and immunosuppressive thiopurines such as 6-mercaptopurine, 6-thioguanine, and azathioprine. Thiopurine drugs have a relatively narrow therapeutic index and are capable of causing life-threatening toxicity, most often myelosuppression (Sahasranaman et al., 2008). TPMT genetic polymorphism represents a striking example of the clinical importance of pharmacogenetics. In 2010, 29 different variant TPMT alleles have been described (Ford & Berg, 2010) and this may be associated with large interindividual variations in thiopurine drug toxicity and therapeutic efficacy. Allele frequencies for genetic polymorphism are such that ~1 in 300 Caucasians is homozygous for a defective allele or alleles for the trait of very low activity, ~11% of people are heterozygous and have intermediate activity. Subjects homozygous for low TPMT activity have a high risk of myelosuppression after treatment with standard dose of azathioprine. Generally, TPMT-deficient patients (homozygous mutant) can be treated with 6–10% of the standard dose of thiopurines (Zhou, 2006). TPMT shows the highest level of expression in liver and kidney and the physiological role of this enzyme, despite extensive investigation, remains unclear.

2.5.4 As-methylation

Arsenic is a well-known naturally occurring metalloid which is considered as a multiorgan human carcinogen. Occupational exposure to arsenic occurs in the smelting industry and

during the manufacture of pesticides, herbicides, and other agricultural products. Arsenic plays a dual role as environmental carcinogenic pollutant and as a successful anticancer drug against promyelocytic leukemia (Wood et al., 2006). Its metabolism proceeds via a complicated enzymatic pathway, acting both as detoxification and producing more toxic intermediates. Methylation is an important reaction in the biotransformation of arsenic. Liver is considered to be the primary site for the methylation of inorganic arsenic (iAs) and *arsenic (+3 oxidation state) methyltransferase (AS3MT)* is shown to be critical specifically for the arsenic metabolism, and thus may be pharmacologically important as well. Methylated and dimethylated arsenic are the major urinary metabolites in human and many other species (Li et al., 2005). Two reaction schemes (Fig. 7) have been developed to describe the individual steps in the enzymatically catalysed conversion of iAs to methylated metabolites (Thomas, 2007). Although pentavalent methylated arsenicals (MAs^V, DMAs^V, TMs^V) are less toxic than inorganic ones (iAs^V, iAs^{III}), the trivalent intermediates formed during the methylation process (MAs^{III}, DMAs^{III}) are much more cytotoxic and genotoxic (Hughes, 2009).

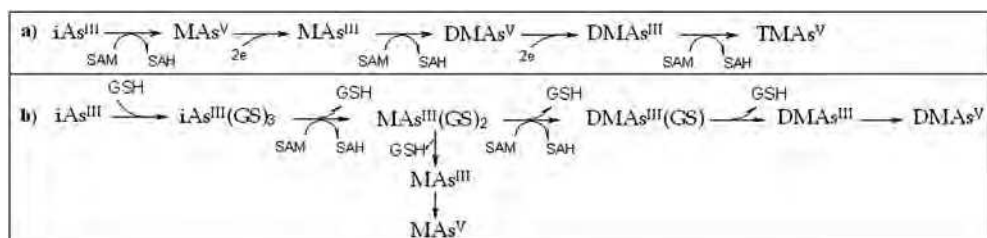


Fig. 7. Alternative schemes for the conversion of inorganic arsenic (iAs) into methylated metabolites. (a) Scheme for the oxidative methylation of arsenicals in which reduction of oxidized arsenicals is interposed between each methylation reaction. (b) Scheme for methylation of arsenic involving formation of arsenic-glutathione (GSH) complex. SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine (According to Thomas, 2007).

Several single nucleotide polymorphisms in exons and introns in this gene are reported to be related to inter-individual variation in the arsenic metabolism (Fujihara et al., 2010). Polymorphism in AS3MT may influence arsenic metabolism and potentially susceptibility to its toxic and carcinogenic effects.

2.6 Amino acid conjugation reactions

The first description of glycine conjugation was published in 1842 by Keller. Xenobiotics containing a carboxyl group (-COOH) are widely used as drugs (for example simvastatin, valproic acid, or acetylsalicylic acid), herbicides, insecticides, and food preservatives. In addition, many xenobiotics are readily metabolized to carboxylic acids which may then be conjugated with amino acids. The ability of xenobiotics to undergo amino acid conjugation depends on the steric hindrance around the carboxylic acid group, and on substituents of the aromatic ring or aliphatic side chain. Amino acid conjugation is the most important route of detoxification, not only for many xenobiotic carboxylic acids but also for endogenous acids. It is known that amino acid conjugation of exogenous carboxylic acids occurs in a two-step process (Reilly et al., 2007). Amino acids conjugation of carboxylic acids

is a special form of acetylation and leads to amide bond formation. The most common amino acid in such reactions is glycine, and its prototypical substrate is benzoic acid, more precisely its benzoyl-CoA cofactor (Fig. 8). Bile acids are also conjugated by a similar sequence of reactions involving a microsomal cholyl-CoA synthetase and a cytosolic enzyme bile acid-CoA: amino acid *N*-acyltransferase (Falany et al., 1994). In relation to xenobiotic carboxylic acids, amino acid conjugation involves enzymes located principally in the mitochondria of liver and kidney while conjugation of bile acids is extramitochondrial, involving enzymes located in the endoplasmic reticulum and peroxisomes (Reilly et al., 2007; Knights et al., 2007).

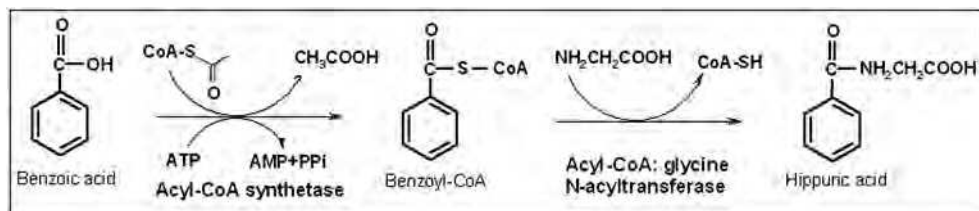


Fig. 8. Conjugation of a xenobiotic with amino acid, formation of hippuric acid.

Glycine and glutamate appear to be the most common acceptors of amino acids in mammals. In humans, more than 95% of bile acids are *N*-acyl amidates with glycine or taurine. Although products of amino acid conjugation are considered to be metabolically stable and nontoxic, it has been suggested that the first reaction of amino acid conjugation leads in some cases to formation of potentially toxic intermediates. This toxification pathway involves conjugation of *N*-hydroxy aromatic amines with the carboxylic acid group of serine and proline. Amino acid activated by aminoacyl-tRNA-synthetase (Fig. 9) subsequently reacts with an aromatic hydroxylamine to form *N*-ester that can degrade to produce a reactive nitrenium ion (Parkinson, 2001). In general, the toxicity of nitrenium ions is clinically relevant since these electrophiles possessing DNA-binding ability are responsible for carcinogenicity of aromatic amines.

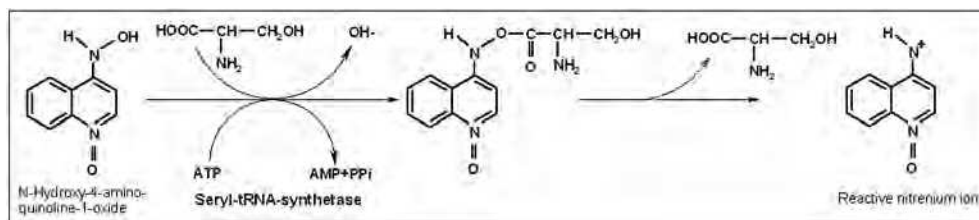


Fig. 9. Conjugation of a xenobiotic with amino acid, formation of electrophilic nitrenium ion.

3. Conclusion

Xenobiotic biotransformation is a key mechanism for maintaining homeostasis during exposure to various xenobiotics, such as drugs, industrial chemicals, or food procarcinogens. In humans and other mammals, the liver is the major site of expression of xenobiotic-metabolising enzymes, but extrahepatically localized enzymes also appear to be of great importance. In the intestine for example, several drug metabolising enzymes are

presumed to decrease the bioavailability of orally administered drugs or to activate environmental carcinogens. Phase II of metabolism may or may not be preceded by Phase I reactions. Phase II enzymes undoubtedly play an important role in the detoxification of various xenobiotics. Furthermore, they significantly contribute to maintaining of homeostasis by binding, transport or inactivation of biologically active compounds such as hormones, bile acids, or other mediators. In contrast to their beneficial effects, these enzymes also participate in formation of reactive intermediates of various compounds. The most-discussed example of toxification reactions is the conjugation of *N*-hydroxy aromatic amines. These compounds undergo activation to toxic metabolites by numerous reactions, including *N*-glucuronidation by UGTs, *O*-acetylation by NATs, *O*-sulfonation by SULTs, and conjugation with amino acids by aminoacyl-tRNA-synthetase. The newly formed reactive electrophilic nitrenium and carbonium ions can act as carcinogens and mutagens due to covalent binding to DNA or to other biomolecules. Genetic polymorphisms of Phase II enzymes is another noteworthy issue. Impaired metabolism of drugs due to genetically based dysfunction of competent enzymes may lead to manifestation of toxic effects of clinically used drugs. Moreover, it is evident that genetic polymorphisms in these enzymes are responsible for the development of a number of neurological disorders or cancers. In conclusion, Phase II enzymes are an interesting research field since they play an essential role in the metabolism of hundreds of foreign compounds as well as in regulation of metabolism and disposition of various endogenous biologically active substances and thus maintaining homeostasis in the human body.

4. Acknowledgment

Infrastructural part of this project has been supported by CZ.1.05/2.1.00/01.0030 (Biomedreg).

5. References

- Adam, P.J.; Berry, J.; Loader, J.A.; Tyson, K.L.; Craggs, G.; Smith, P.; De Belin, J.; Steers, G.; Pezzella, F.; Sachsenmeir, K.F.; Stamps, A.C.; Herath, A.; Sim, E.; O'Hare, M.J.; Harris, A.L. & Terrett, J.A. (2003). Arylamine *N*-acetyltransferase-1 is highly expressed in breast cancers and conveys enhanced growth and resistance to etoposide in vitro. *Molecular Cancer Research*, Vol.1, No.11, (September 2003), pp.826–835, ISSN 1541-7786
- Agúndez, J.A. (2008). Polymorphisms of human *N*-acetyltransferases and cancer risk. *Current Drug Metabolism*, Vol.9, No.6, (July 2008), pp.520–531, ISSN 1389-2002
- Arslan, S.; Silig, Y. & Pinarbasi, H. (2009). An investigation of the relationship between *SULT1A1* Arg(213)His polymorphism and lung cancer susceptibility in a Turkish population. *Cell Biochemistry and Function*, Vol.27, No.4, (June 2009), pp.211–215, ISSN 0263-6484
- Autrup, J.L.; Hokland, P.; Pedersen, L. & Autrup, H. (2002). Effect of glutathione *S*-transferases on the survival of patients with acute myeloid leukaemia. *European Journal of Pharmacology*, Vol.438, No.1–2, (March 2002), pp.15–18, ISSN 0014-2999
- Bardakci, F.; Arslan, S.; Bardakci, S.; Binatli, A.O. & Budak, M. (2008). Sulfotransferase 1A1 (*SULT1A1*) polymorphism and susceptibility to primary brain tumors. *Journal of*

- Cancer Research and Clinical Oncology*, Vol.134, No.1, (January 2008), pp.109-114, ISSN 0171-5216
- Beland, F.A. & Kadlubar, F.F. (1985). Formation and persistence of arylamine DNA adducts in vivo. *Environmental Health Perspectives*, Vol.62, (October 1985), pp. 19-30, ISSN 0091-6765
- Blanchard, R.L.; Freimuth, R.R.; Buck, J.; Weinshilboum, R.M. & Coughtrie, M.W. (2004). A proposed nomenclature system for the cytosolic sulfotransferase (SULT) superfamily. *Pharmacogenetics*, Vol.14, No.3, (March 2004), pp.199-211, ISSN 0960-314X
- Blum, M.; Grant, D.M.; McBride, W.; Heim, M. & Meyer, U.A. (1990). Human arylamine N-acetyltransferase genes: isolation, chromosomal localization, and functional expression. *DNA and Cell Biology*, Vol.9, No.3, (April 1990), pp.193-203, ISSN 1044-5498
- Boettcher, M.I.; Schettgen, T.; Kütting, B.; Pischetsrieder, M. & Angerer, J. (2005). Mercapturic acids of acrylamide and glycidamide as biomarkers of the internal exposure to acrylamide in the general population. *Mutation Research*, Vol.580, No.1-2, (February 2005), pp.167-176, ISSN 0027-5107
- Bosio, A.; Binczek, E.; Le Beau, M.M.; Fernald, A.A. & Stoffel, W. (1996). The human gene CGT encoding the UDP-galactose ceramide galactosyl transferase (cerebroside synthase): cloning, characterization, and assignment to human chromosome 4, band q26. *Genomics*, Vol.34, No.1, (May 1996), pp.69-75, ISSN 0888-7543
- Bresell A, Weinander R, Lundqvist G, Raza H, Shimoji M, Sun TH, Balk L, Wiklund R, Eriksson J, Jansson C, Persson B, Jakobsson PJ, Morgenstern R. (2005). Bioinformatic and enzymatic characterization of the MAPEG superfamily. *The FEBS Journal*, Vol.272, No.7, (April 2005), pp.1688-1703, ISSN 1742-464X
- Brockton, N.; Little, J.; Sharp, L. & Cotton, S.C. (2000). N-acetyltransferase polymorphisms and colorectal cancer: a HuGE review. *American Journal of Epidemiology*, Vol.151, No.9, (May 2000), pp.846-861, ISSN 0002-9262
- Buhl, A.E.; Waldon, D.J.; Baker, C.A. & Johnson, G.A. (1990). Minoxidil sulfate is the active metabolite that stimulates hair follicles. *The Journal of Investigative Dermatology*, Vol.95, No.5, (November 1990), pp.553-557, ISSN 0022-202X
- Burchell, B.; Brierley, C.H. & Rance, D. (1995). Specificity of human UDP-glucuronosyltransferases and xenobiotic glucuronidation. *Life Sciences*, Vol.57, No.20, (1995), pp.1819-1831, ISSN 0024-3205
- Butcher, N.J.; Boukouvala, S.; Sim, E. & Minchin R.F. (2002). Pharmacogenetics of the arylamine N-acetyltransferases. *The Pharmacogenomics Journal*, Vol.2, No.1, (2002), pp.30-42, ISSN 1470-269X
- Chen, M.; Xia, B.; Chen, B.; Guo, Q.; Li, J.; Ye, M. & Hu, Z. (2007). N-acetyltransferase 2 slow acetylator genotype associated with adverse effects of sulphasalazine in the treatment of inflammatory bowel disease. *Canadian Journal of Gastroenterology*, Vol.21, No.3, (March 2007), pp.155-158, ISSN 0835-7900
- Coffman, B.L.; King, C.D.; Rios, G.R. & Tephly, T.R. (1998). The glucuronidation of opioids, other xenobiotics, and androgens by human UGT2B7Y(268) and UGT2B7H(268). *Drug Metabolism and Disposition*, Vol.26, No.1, (January 1998), pp.73-77, ISSN 0090-9556

- Cole, G.B.; Keum, G.; Liu, J.; Small, G.W.; Satyamurthy, N.; Kepe, V. & Barrio, J.R. (2010). Specific estrogen sulfotransferase (SULT1E1) substrates and molecular imaging probe candidates. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.107, No.14, (April 2010), pp.6222-6227, ISSN 0027-8424
- Collier, A.C.; Ganley, N.A.; Tingle, M.D.; Blumenstein, M.; Marvin, K.W.; Paxton, J.W.; Mitchell, M.D. & Keelan, J.A. (2002). UDP-glucuronosyltransferase activity, expression and cellular localization in human placenta at term. *Biochemical Pharmacology*, Vol.63, No.3, (February 2002), pp.409-419, ISSN 0006-2952
- Comer, K.A.; Falany, J.L. & Falany, C.N. (1993). Cloning and expression of human liver dehydroepiandrosterone sulphotransferase. *The Biochemical Journal*, Vol.289, No. Pt 1, (January 1993), pp.233-240, ISSN 0264-6021
- Commandeur, J.N.; Stijntjes, G.J. & Vermeulen, N.P. (1995). Enzymes and transport systems involved in the formation and disposition of glutathione S-conjugates. Role in bioactivation and detoxication mechanisms of xenobiotics. *Pharmacological Reviews*, Vol.47, No.2, (June 1995), pp. 271-330, ISSN 0031-6997
- Court, M.H.; Duan, S.X.; von Moltke, L.L.; Greenblatt, D.J.; Patten, C.J.; Miners, J.O. & Mackenzie PI. (2001). Interindividual variability in acetaminophen glucuronidation by human liver microsomes: identification of relevant acetaminophen UDP-glucuronosyltransferase isoforms. *The Journal of Pharmacology and Experimental Therapeutics*, Vol.299, No.3, (December 2001), pp.998-1006, ISSN 0022-3565
- Court, M.H.; Hao, Q.; Krishnaswamy, S.; Bekaii-Saab, T.; Al-Rohaimi, A.; von Moltke, L.L. & Greenblatt, D.J. (2004). UDP-glucuronosyltransferase (UGT) 2B15 pharmacogenetics: UGT2B15 D85Y genotype and gender are major determinants of oxazepam glucuronidation by human liver. *The Journal of Pharmacology and Experimental Therapeutics*, Vol.310, No.2, (August 2004), pp.656-665, ISSN 0022-3565
- Crettol, S.; Petrovic, N. & Murray, M. (2010). Pharmacogenetics of phase I and phase II drug metabolism. *Current Pharmaceutical Design*, Vol.16, No.2, (2010), pp.204-219, ISSN 1381-6128
- Dagnino-Subiabre, A.; Cassels, B.K.; Baez, S.; Johansson, A.S.; Mannervik, B. & Segura-Aguilar, J. (2000). Glutathione transferase M2-2 catalyzes conjugation of dopamine and dopa o-quinones. *Biochemical and Biophysical Research Communications*, Vol.274, No.1, (July 2000), pp.32-36, ISSN 0006-291X
- Dellinger, R.W.; Fang, J.L.; Chen, G.; Weinberg, R. & Lazarus, P. (2006). Importance of UDP-glucuronosyltransferase 1A10 (UGT1A10) in the detoxification of polycyclic aromatic hydrocarbons: decreased glucuronidative activity of the UGT1A10139Lys isoform. *Drug Metabolism and Disposition*, Vol.34, No.6, (January 2006), pp.943-949, ISSN 0090-9556
- Dupret, J.M. & Rodrigues-Lima F. (2005). Structure and regulation of the drug-metabolizing enzymes arylamine N-acetyltransferases. *Current Medicinal Chemistry*, Vol.12, No.3, (2005), pp.311-318, ISSN 0929-8673
- Falany, C.N.; Johnson, M.R.; Barnes, S. & Diasio, R.B. (1994). Glycine and taurine conjugation of bile acids by a single enzyme. Molecular cloning and expression of human liver bile acid CoA:amino acid N-acyltransferase. *The Journal of Biological Chemistry*, Vol.269, No.30, (July 1994), pp.19375-19379, ISSN 0021-9258

- Falany, C.N.; Xie, X.; Wang, J.; Ferrer, J. & Falany, J.L. (2000). Molecular cloning and expression of novel sulphotransferase-like cDNAs from human and rat brain. *The Biochemical Journal*, Vol.346, No.Pt 3, (March 2000), pp.857-864, ISSN 0264-6021
- Feng, J.; Sun, J.; Wang, M.Z.; Zhang, Z.; Kim, S.T.; Zhu, Y.; Sun, J. & Xu, J. (2010). Compilation of a comprehensive gene panel for systematic assessment of genes that govern an individual's drug responses. *Pharmacogenomics*, Vol.11, No.10, (October 2010), pp.1403-1425, ISSN 1462-2416
- Ford, L.T. & Berg, J.D. (2010). Thiopurine S-methyltransferase (TPMT) assessment prior to starting thiopurine drug treatment; a pharmacogenomic test whose time has come. *Journal of Clinical Pathology*, Vol.63, No.4, (April 2010), pp.288-295, ISSN 0021-9746
- Fujihara, J.; Soejima, M.; Yasuda, T.; Koda, Y.; Agusa, T.; Kunito, T.; Tongu, M.; Yamada, T. & Takeshita, H. (2010). Global analysis of genetic variation in human arsenic (+3 oxidation state) methyltransferase (AS3MT). *Toxicology and Applied Pharmacology*, Vol.243, No.3, (March 2010), pp.292-299, ISSN 0041-008X
- Fujita, K.; Nagata, K.; Ozawa, S.; Sasano, H. & Yamazoe, Y. (1997). Molecular cloning and characterization of rat ST1B1 and human ST1B2 cDNAs, encoding thyroid hormone sulfotransferases. *Journal of Biochemistry*, Vol.122, No.5, (November 1997), pp.1052-1061, ISSN 0021-924X
- Gamage, N.; Barnett, A.; Hempel, N.; Duggleby, R.G.; Windmill, K.F.; Martin, J.L. & McManus, M.E. (2006). Human sulfotransferases and their role in chemical metabolism. *Toxicological Sciences*, Vol.90, No.1, (March 2006), pp.5-22, ISSN 1096-0929
- Gilissen, R.A.; Bamforth, K.J.; Stavenuiter, J.F.; Coughtrie, M.W. & Meerman, J.H. (1994). Sulfation of aromatic hydroxamic acids and hydroxylamines by multiple forms of human liver sulfotransferases. *Carcinogenesis*, Vol.15, No.1, (January 1994), pp.39-45, ISSN 0143-3334
- Ginsberg, G.; Smolenski, S.; Neafsey, P.; Hattis, D.; Walker, K.; Guyton, K.Z.; Johns, D.O. & Sonawane, B. (2009). The influence of genetic polymorphisms on population variability in six xenobiotic-metabolizing enzymes. *Journal of Toxicology and Environmental Health Part B: Critical Reviews*, Vol.12, No.5-6, (2009), pp.307-333, ISSN 1093-7404
- Glatt, H.; Boeing, H.; Engelke, C.E.; Ma, L.; Kuhlow, A.; Pabel, U.; Pomplun, D.; Teubner, W. & Meinl, W. (2001). Human cytosolic sulphotransferases: genetics, characteristics, toxicological aspects. *Mutation Research*, Vol.482, No.1-2, (October 2001), pp.27-40, ISSN 0027-5107
- Glatt, H. & Meinl, W. (2004). Pharmacogenetics of soluble sulfotransferases (SULTs). *Naunyn-Schmiedeberg's Archives of Pharmacology*, Vol.369, No.1, (January 2004), pp.55-68, ISSN 0028-1298
- Grant, D.M.; Mörike, K.; Eichelbaum, M. & Meyer, U.A. (1990). Acetylation pharmacogenetics. The slow acetylator phenotype is caused by decreased or absent arylamine N-acetyltransferase in human liver. *The Journal of Clinical Investigation*, Vol.85, No.3, (March 1990), pp.968-972, ISSN 0021-9738
- Guillemette, C. (2003). Pharmacogenomics of human UDP-glucuronosyltransferase enzymes. *The Pharmacogenomics Journal*, Vol.3, No.3, (2003), pp.136-158, ISSN 1470-269X

- Haavik, J.; Blau, N. & Thöny, B. (2008). Mutations in human monoamine-related neurotransmitter pathway genes. *Human Mutation*, Vol.29, No.7, (July 2008), pp.891-902, ISSN 1059-7794
- Habuchi, O. (2000). Diversity and functions of glycosaminoglycan sulfotransferases. *Biochimica et Biophysica Acta*, Vol.1474, No.2, (April 2000), pp.115-127, ISSN 0006-3002
- Hanioka, N.; Naito, T. & Narimatsu, S. (2008). Human UDP-glucuronosyltransferase isoforms involved in bisphenol A glucuronidation. *Chemosphere*, Vol.74, No.1, (December 2008), pp.33-36, ISSN 0045-6535
- Hayes, J.D. & Strange, R.C. (2000). Glutathione S-transferase polymorphisms and their biological consequences. *Pharmacology*, Vol.61, No.3, (September 2000), pp.154-166, ISSN 0031-7012
- Hayes, J.D.; Flanagan, J.U. & Jowsey, I.R. (2005). Glutathione transferases. *Annual Review of Pharmacology and Toxicology*, Vol.45, (2005), pp.51-88, ISSN 0362-1642
- Hehonah, N.; Zhu, X.; Brix, L.; Bolton-Grob, R.; Barnett, A.; Windmill, K. & McManus, M. (1999). Molecular cloning, expression, localisation and functional characterisation of a rabbit SULT1C2 sulfotransferase. *The International Journal of Biochemistry & Cell Biology*, Vol.31, No.8, (August 1999), pp.869-882, ISSN 1357-2725
- Hein, D.W.; McQueen, C.A.; Grant, D.M.; Goodfellow, G.H.; Kadlubar, F.F. & Weber, W.W. (2000). Pharmacogenetics of the arylamine N-acetyltransferases: a symposium in honor of Wendell W. Weber. *Drug Metabolism and Disposition*, Vol.28, No.12, (December 2000), pp.1425-1432, ISSN 0090-9556
- Hempel, N.; Gamage, N.; Martin, J.L. & McManus, M.E. (2007). Human cytosolic sulfotransferase SULT1A1. *The International Journal of Biochemistry & Cell Biology*, Vol.39, No.4, (October 2006), pp.685-689, ISSN 1357-2725
- Her, C.; Kaur, G.P.; Athwal, R.S. & Weinshilboum, R.M. (1997). Human sulfotransferase SULT1C1: cDNA cloning, tissue-specific expression, and chromosomal localization. *Genomics*, Vol.41, No.3, (May 1997), pp.467-470, ISSN 0888-7543
- Hickman, D.; Pope, J.; Patil, S.D.; Fakis, G.; Smelt, V.; Stanley, L.A.; Payton, M.; Unadkat, J.D. & Sim, E. (1998). Expression of arylamine N-acetyltransferase in human intestine. *Gut*, Vol.42, No.3, (March 1998), pp.402-409, ISSN 0017-5749
- Hodgson, E. (2004). *A textbook of modern toxicology*, John Wiley & Sons, Inc., Retrieved from <http://faculty.ksu.edu.sa/73069/Documents/Toxicology.pdf>
- Huang, S.K.; Chiu, A.W.; Pu, Y.S.; Huang, Y.K.; Chung, C.J.; Tsai, H.J.; Yang, M.H.; Chen, C.J. & Hsueh, Y.M. (2009). Arsenic methylation capability, myeloperoxidase and sulfotransferase genetic polymorphisms, and the stage and grade of urothelial carcinoma. *Urologia Internationalis*, Vol.82, No.2, (March 2009), pp.227-234, ISSN 0042-1138
- Hughes, M.F. (2009). Arsenic methylation, oxidative stress and cancer--is there a link? *The Journal of the National Cancer Institute*, Vol.101, No.24, (December 2009), pp.1660-1661, ISSN 0027-8874
- Javitt, N.B.; Lee, Y.C.; Shimizu, C.; Fuda, H. & Strott, C.A. (2001). Cholesterol and hydroxycholesterol sulfotransferases: identification, distinction from dehydroepiandrosterone sulfotransferase, and differential tissue expression. *Endocrinology*, Vol.142, No.7, (July 2001), pp.2978-2984, ISSN 0013-7227

- Ji, Y.; Salavaggione, O.E.; Wang, L.; Adjei, A.A.; Eckloff, B.; Wieben, E.D. & Weinshilboum, R.M. (2005). Human phenylethanolamine N-methyltransferase pharmacogenomics: gene re-sequencing and functional genomics. *Journal of Neurochemistry*, Vol.95, No.6, (December 2005), pp.1766-1776, ISSN 0022-3042
- Ji, Y.; Snyder, E.M.; Fridley, B.L.; Salavaggione, O.E.; Moon, I.; Batzler, A.; Yee, V.C.; Schaid, D.J.; Joyner, M.J.; Johnson, B.D. & Weinshilboum, R.M. (2008). Human phenylethanolamine N-methyltransferase genetic polymorphisms and exercise-induced epinephrine release. *Physiological Genomics*, Vol.33, No.3, (May 2008), pp.323-332, ISSN 1094-8341
- Kadacol, A.; Ghosh, S.S.; Sappal, B.S.; Sharma, G.; Chowdhury, J.R. & Chowdhury, N.R. (2000). Genetic lesions of bilirubin uridine-diphosphoglucuronate glucuronosyltransferase (UGT1A1) causing Crigler-Najjar and Gilbert syndromes: correlation of genotype to phenotype. *Human Mutation*, Vol.16, No.4, (October 2000), pp.297-306, ISSN 1059-7794
- Kawamura, A.; Graham, J.; Mushtaq, A.; Tsiftoglou, S.A.; Vath, G.M.; Hanna, P.E.; Wagner, C.R. & Sim, E. (2005). Eukaryotic arylamine N-acetyltransferase. Investigation of substrate specificity by highthroughput screening. *Biochemical Pharmacology*, Vol.69, No.2, (January 2005), pp.347-359, ISSN 0006-2952
- Kemp, D.C.; Fan, P.W. & Stevens, J.C. (2002). Characterization of raloxifene glucuronidation in vitro: contribution of intestinal metabolism to presystemic clearance. *Drug Metabolism and Disposition*, Vol.30, No.6, (June 2002), pp.694-700, ISSN 0090-9556
- Kerdar, R.S.; Dehner, D. & Wild, D. (1993). Reactivity and genotoxicity of arylnitrenium ions in bacterial and mammalian cells. *Toxicology Letters*, Vol.67, No.1-3, (April 1993), pp.73-85, ISSN 0378-4274
- Kiang, T.K.; Ensom, M.H. & Chang, T.K. (2005). UDP-glucuronosyltransferases and clinical drug-drug interactions. *Pharmacology & Therapeutics*, Vol.106, No.1, (April 2005), pp.97-132, ISSN 0163-7258
- King, C.D.; Rios, G.R.; Assouline, J.A. & Tephly, T.R. (1999). Expression of UDPglucuronosyltransferases (UGTs) 2B7 and 1A6 in the human brain and identification of 5-hydroxytryptamine as a substrate. *Archives of Biochemistry and Biophysics*, Vol.365, No.1, (May1999), pp.156-162, ISSN 0003-9861
- Klaassen, C.D. & Boles, J.W. (1997). Sulfation and sulfotransferases 5: the importance of 3'-phosphoadenosine 5'-phosphosulfate (PAPS) in the regulation of sulfation. *The FASEB Journal*, Vol.11, No.6, (May 1997), pp.404-418, ISSN 0892-6638
- Knights, K.M.; Sykes, M.J. & Miners, J.O. (2007). Amino acid conjugation: contribution to the metabolism and toxicity of xenobiotic carboxylic acids. *Expert Opinion on Drug Metabolism & Toxicology*, Vol.3, No.2, (April 2007), pp.159-168, ISSN 1742-5255
- Knights, K.M.; Winner, L.K.; Elliot, D.J.; Bowalgaha, K. & Miners, J.O. (2009). Aldosterone glucuronidation by human liver and kidney microsomes and recombinant UDP-glucuronosyltransferases: inhibition by NSAIDs. *British Journal of Clinical Pharmacology*, Vol.68, No.3, (September 2009), pp.402-412, ISSN 0306-5251
- Kunugi, H.; Nanko, S.; Ueki, A.; Otsuka, E.; Hattori, M.; Hoda, F.; Vallada, H.P.; Arranz, M.J. & Collier, D.A. (1997). High and low activity alleles of catechol-O-methyltransferase gene: ethnic difference and possible association with Parkinson's disease. *Neuroscience Letters*, Vol.221, No.2-3, (January 1997), pp.202-204, ISSN 0304-3940

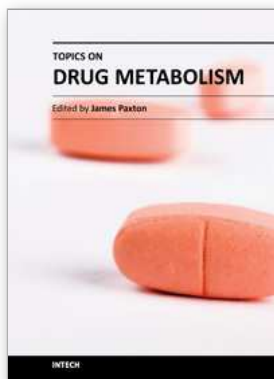
- Ladero, J.M. (2008). Influence of polymorphic N-acetyltransferases on non-malignant spontaneous disorders and on response to drugs. *Current Drug Metabolism*, Vol.9, No.6, (July 2008), pp.532-537, ISSN 1389-2002
- Lammer, E.J.; Shaw, G.M.; Iovannisci, D.M. & Finnell, R.H. (2004). Periconceptual multivitamin intake during early pregnancy, genetic variation of acetyl-N-transferase 1 (NAT1), and risk for orofacial clefts. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, Vol.70, No.11, (November 2004), pp.846-852, ISSN 1542-0752
- Landi, S. (2000). Mammalian class theta GST and differential susceptibility to carcinogens: a review. *Mutation Research*, Vol.463, No.3, (October 2000), pp.247-283, ISSN 0027-5107
- Li, J.; Waters, S.B.; Drobna, Z.; Devesa, V.; Styblo, M. & Thomas, D.J. (2005). Arsenic (+3 oxidation state) methyltransferase and the inorganic arsenic methylation phenotype. *Toxicology and Applied Pharmacology*, Vol.204, No.2, (April 2005), pp.164-169, ISSN 0041-008X
- Lin, J.H. & Wong, B.K. (2002). Complexities of glucuronidation affecting in vitro in vivo extrapolation. *Current Drug Metabolism*, Vol.3, No.6, (December 2002), pp.623-646, ISSN 1389-2002
- Lindsay, J.; Wang, L.L.; Li, Y. & Zhou, S.F. (2008). Structure, function and polymorphism of human cytosolic sulfotransferases. *Current Drug Metabolism*, Vol.9, No.2, (February 2008), pp.99-105, ISSN 1389-2002
- Mackenzie, P.I.; Gregory, P.A.; Gardner-Stephen, D.A.; Lewinsky, R.H.; Jorgensen, B.R.; Nishiyama, T.; Xie, W. & Radominska-Pandya, A. (2003). Regulation of UDP glucuronosyltransferase genes. *Current Drug Metabolism*, Vol.4, No.3, (June 2003), pp.249-257, ISSN 1389-2002
- Mackenzie, P.I.; Rogers, A.; Treloar, J.; Jorgensen, B.R.; Miners, J.O. & Meech, R. (2008). Identification of UDP glycosyltransferase 3A1 as a UDP N-acetylglucosaminyltransferase. *The Journal of Biological Chemistry*, Vol.283, No.52, (December 2008), pp.36205-36210, ISSN 0021-9258
- Maintz, L. & Novak, N. (2007). Histamine and histamine intolerance. *The American Journal of Clinical Nutrition*, Vol.85, No.5, (May 2007), pp.1185-1196, ISSN 0002-9165
- Meinl, W.; Meerman, J.H. & Glatt, H. (2002). Differential activation of promutagens by alloenzymes of human sulfotransferase 1A2 expressed in *Salmonella typhimurium*. *Pharmacogenetics*, Vol.12, No.9, (December 2002), pp.677-689, ISSN 0960-314X
- Minchin, R.F. (1995). Acetylation of p-aminobenzoyleglutamate, a folic acid catabolite, by recombinant human arylamine N-acetyltransferase and U937 cells. *The Biochemical Journal*, Vol.307, No.Pt 1, (April 1995), pp.1-3, ISSN 0264-6021
- Miners, J.O. & Mackenzie, P.I. (1991). Drug glucuronidation in humans. *Pharmacology & Therapeutics*, Vol.51, No.3, (1991), pp.347-369, ISSN 0163-7258
- Miners, J.O.; Knights, K.M.; Houston, J.B. & Mackenzie, P.I. (2006). In vitro-in vivo correlation for drugs and other compounds eliminated by glucuronidation in humans: pitfalls and promises. *Biochemical Pharmacology*, Vol.71, No.11, (May 2006), pp.1531-1539, ISSN 0006-2952
- Mizuma, T. (2009). Intestinal glucuronidation metabolism may have a greater impact on oral bioavailability than hepatic glucuronidation metabolism in humans: a study with

- raloxifene, substrate for UGT1A1, 1A8, 1A9, and 1A10. *International Journal of Pharmaceutics*, Vol.378, No.1-2, (August 2009), pp.140-141, ISSN 0378-5173
- Monaghan, G.; Ryan, M.; Seddon, R.; Hume, R. & Burchell, B. (1996). Genetic variation in bilirubin UDP-glucuronosyltransferase gene promoter and Gilbert's syndrome. *Lancet*, Vol.347, No.9001, (March 1996), pp.578-581, ISSN 0140-6736
- Morel, F.; Rauch, C.; Petit, E.; Piton, A.; Theret, N.; Coles, B. & Guillouzo, A. (2004). Gene and protein characterization of the human glutathione S-transferase kappa and evidence for a peroxisomal localization. *The Journal of Biological Chemistry*, Vol.279, No.16. (April 2004), pp.16246-16253, ISSN 0021-9258
- Mutschler, E.; Gilfrich, H.J.; Knauf, H.; Möhrke, W. & Völger, K.D. (1983). Pharmacokinetics of triamterene. *Clinical and Experimental Hypertension. Part A, Theory and Practice*, Vol.5, No.2, (1983), pp.249-269, ISSN 0730-0077
- Pacifici, G.M.; Bencini, C. & Rane, A. (1986). Acetyltransferase in humans: development and tissue distribution. *Pharmacology*, Vol.32, No.5, (1986), pp.283-91, ISSN 0031-7012
- Pariente-Khayat, A.; Pons, G.; Rey, E.; Richard, M.O.; D'Athis, P.; Moran, C.; Badoual, J. & Olive, G. (1991). Caffeine acetylator phenotyping during maturation in infants. *Pediatric Research*, Vol.29, No.5, (May 1991), pp.492-495, ISSN 0031-3998
- Park, T.W.; Yoon, K.S.; Kim, J.H.; Park, W.Y.; Hirvonen, A. & Kang, D. (2002). Functional catechol-O-methyltransferase gene polymorphism and susceptibility to schizophrenia. *European Neuropsychopharmacology*, Vol.12, No.4, (August 2002), pp.299-303, ISSN 0924-977X
- Parkinson, A. (2001). *Casarett and Doull's Toxicology—the Basic Science of Poisons (6th Edition)*, McGraw-Hill, Retrieved from http://www.knovel.com/web/portal/basic_search/display?_EXT_KNOVEL_DISPLAY_bookid=956
- Patten, C.J. (2006). New technologies for assessing UDP-glucuronosyltransferase (UGT) metabolism in drug discovery and development. *Drug Discovery Today: Technologies*, Vol.3, No.1, (Spring 2006), pp.73-78, ISSN 1740-6749
- Popp, W.; Vahrenholz, C.; Przygoda, H.; Brauksiepe, A.; Goch, S.; Müller, G.; Schell, C. & Norpoth, K. (1994). DNA-protein cross-links and sister chromatid exchange frequencies in lymphocytes and hydroxyethyl mercapturic acid in urine of ethylene oxide-exposed hospital workers. *International Archives of Occupational and Environmental Health*, Vol.66, No.5, (1994), pp.325-332, ISSN 0340-0131
- Preuss, C.V.; Wood, T.C.; Szumlanski, C.L.; Raftogianis, R.B.; Otterness, D.M.; Girard, B., Scott, M.C. & Weinshilboum, R.M. (1998). Human histamine N-methyltransferase pharmacogenetics: common genetic polymorphisms that alter activity. *Molecular Pharmacology*, Vol.53, No.4, (April 1998), pp.708-717, ISSN 0026-895X
- Reilly, S.J.; O'Shea, E.M.; Andersson, U.; O'Byrne, J.; Alexson, S.E. & Hunt, M.C. (2006). A peroxisomal acyltransferase in mouse identifies a novel pathway for taurine conjugation of fatty acids. *The FASEB Journal*, Vol.21, No.1, (January 2007), pp.99-107, ISSN 0892-6638
- Riches, Z.; Stanley, E.L.; Bloomer, J.C. & Coughtrie, M.W. (2009). Quantitative evaluation of the expression and activity of five major sulfotransferases (SULTs) in human tissues: the SULT "pie". *Drug Metabolism and Disposition*, Vol.37, No.11, (November 2009), pp.2255-2261, ISSN 0142-2782

- Robinson, A.; Huttley, G.A.; Booth, H.S. & Board, P.G. (2004). Modelling and bioinformatics studies of the human Kappa-class glutathione transferase predict a novel third glutathione transferase family with similarity to prokaryotic 2-hydroxychromene-2-carboxylate isomerases. *The Biochemical Journal*, Vol.379, No.Pt 3, (May 2004), pp.541-552, ISSN 0264-6021
- Sahasranaman, S.; Howard, D. & Roy, S. (2008). Clinical pharmacology and pharmacogenetics of thiopurines. *European Journal of Clinical Pharmacology*, Vol.64, No.8, (August 2008), pp.753-767, ISSN 0031-6970
- Saito, S.; Iida, A.; Sekine, A.; Miura, Y.; Sakamoto, T.; Ogawa, C.; Kawauchi, S.; Higuchi, S. & Nakamura, Y. (2001). Identification of 197 genetic variations in six human methyltransferase genes in the Japanese population. *Journal of Human Genetics*, Vol.46, No.9, (2001), pp.529-537, ISSN 1434-5161
- Sakakibara, Y.; Yanagisawa, K.; Katafuchi, J.; Ringer, D.P.; Takami, Y.; Nakayama, T.; Suiko, M. & Liu, M.C. (1998). Molecular cloning, expression, and characterization of novel human SULT1C sulfotransferases that catalyze the sulfonation of N-hydroxy-2-acetylaminofluorene. *The Journal of Biological Chemistry*, Vol.273, No.51, (December 1998), pp.33929-33935, ISSN 0021-9258
- Senggunprai, L.; Yoshinari, K. & Yamazoe, Y. (2009). Selective role of sulfotransferase 2A1 (SULT2A1) in the N-sulfoconjugation of quinolone drugs in humans. *Drug Metabolism and Disposition*, Vol.37, No.8, (August 2009), pp.1711-1717, ISSN 0090-9556
- Sherratt, P.J.; Pulford, D.J.; Harrison, D.J.; Green, T. & Hayes, J.D. (1997). Evidence that human class Theta glutathione S-transferase T1-1 can catalyse the activation of dichloromethane, a liver and lung carcinogen in the mouse. Comparison of the tissue distribution of GST T1-1 with that of classes Alpha, Mu and Pi GST in human. *The Biochemical Journal*, Vol.326, No.Pt 3, (September 1997), pp.837-846, ISSN 0264-6021
- Sim, E.; Stanley, L.; Gill, E.W. & Jones, A. (1988). Metabolites of procainamide and practolol inhibit complement components C3 and C4. *The Biochemical Journal*, Vol.251, No.2, (April 1988), pp.323-326, ISSN 0264-6021
- Sim, E.; Walters, K. & Boukouvala, S. (2008). Arylamine N-acetyltransferases: from structure to function. *Drug Metabolism Reviews*, Vol.40, No.3, (2008), pp.479-510, ISSN 0360-2532
- Sneitz, N.; Court, M.H.; Zhang, X.; Laajanen, K.; Yee, K.K.; Dalton, P.; Ding, X. & Finel, M. (2009). Human UDP-glucuronosyltransferase UGT2A2: cDNA construction, expression, and functional characterization in comparison with UGT2A1 and UGT2A3. *Pharmacogenetics and Genomics*, [Epub ahead of print], (October 2009), ISSN 1744-6872
- Strassburg, C.P.; Strassburg, A.; Kneip, S.; Barut, A.; Tukey, R.H.; Rodeck, B. & Manns, M.P. (2002). Developmental aspects of human hepatic drug glucuronidation in young children and adults. *Gut*, Vol.50, No.2, (February 2002), pp.259-265, ISSN 0017-5749
- Sutherland, L.; Ebner, T. & Burchell, B. (1993). The expression of UDPglucuronosyltransferases of the UGT1 family in human liver and kidney and in response to drugs. *Biochemical Pharmacology*, Vol.45, No.2, (January 1993), pp.295-301, ISSN 0006-2952

- Sweeney, C.; Ambrosone, C.B.; Joseph, L.; Stone, A.; Hutchins, L.F.; Kadlubar, F.F. & Coles, B.F. (2003). Association between a glutathione S-transferase A1 promoter polymorphism and survival after breast cancer treatment. *International Journal of Cancer*, Vol.103, No.6, (March 2003), pp.810-814, ISSN 0020-7136
- Talalay, P.; De Long, M.J. & Prochaska, H.J. (1988). Identification of a common chemical signal regulating the induction of enzymes that protect against chemical carcinogenesis. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.85, No.21, (November 1988), pp.8261-8265, ISSN 0027-8424
- Taskinen, J.; Ethell, B.T.; Pihlavisto, P.; Hood, A.M.; Burchell, B. & Coughtrie, M.W. (2003). Conjugation of catechols by recombinant human sulfotransferases, UDP-glucuronosyltransferases, and soluble catechol O-methyltransferase: structure-conjugation relationships and predictive models. *Drug Metabolism and Disposition*, Vol.31, No.9, (September 2003), pp.1187-1197, ISSN 0090-9556
- Tessitore, L.; Marengo, B.; Vance, D.E.; Papotti, M.; Mussa, A.; Daidone, M.G. & Costa, A. (2003). Expression of phosphatidylethanolamine N-methyltransferase in human hepatocellular carcinomas. *Oncology*, Vol.65, No.2, (2003), pp.152-158, ISSN 0030-2414
- Thomas, D.J. (2007). Molecular processes in cellular arsenic metabolism. *Toxicology and Applied Pharmacology*, Vol.222, No.3, (August 2007), pp.365-373, ISSN 0041-008X
- Thompson, M.A.; Moon, E.; Kim, U.J.; Xu, J.; Siciliano, M.J. & Weinshilboum, R.M. (1999). Human indolethylamine N-methyltransferase: cDNA cloning and expression, gene cloning, and chromosomal localization. *Genomics*, Vol.61, No.3, (November 1999), pp.285-297, ISSN 0888-7543
- Tukey, R.H. & Strassburg, C.P. (2000). Human UDP-glucuronosyltransferases: metabolism, expression, and disease. *Annual Review of Pharmacology and Toxicology*, Vol.40, (2000), pp.581-616, ISSN 0362-1642
- Tunbridge, E.M.; Harrison, P.J. & Weinberger, D.R. (2006). Catechol-o-methyltransferase, cognition, and psychosis: Val158Met and beyond. *Biological Psychiatry*, Vol.60, No.2, (July 2006), pp.141-151, ISSN 0006-3223
- van Bladeren, P.J. (2000). Glutathione conjugation as a bioactivation reaction. *Chemico-biological Interactions*, Vol.129, No.1-2, (December 2000), pp.61-76, ISSN 0009-2797
- Wang, J.; Falany, J.L. & Falany, C.N. (1998). Expression and characterization of a novel thyroid hormone-sulfating form of cytosolic sulfotransferase from human liver. *Molecular Pharmacology*, Vol.53, No.2, (February 1998), pp.274-282, ISSN 0026-895X
- Wang, T.; Franke, P.; Neidt, H.; Cichon, S.; Knapp, M.; Lichtermann, D.; Maier, W.; Propping, P. & Nothen M.M. (2001). Association study of the lowactivity allele of catechol-O-methyltransferase and alcoholism using a family-based approach. *Molecular Psychiatry*, Vol.6, No.1, (January 2001), pp.109-111, ISSN 1359-4184
- Wang, X.; Chowdhury, J.R. & Chowdhury, N.R. (2006). Bilirubin Metabolism: Applied physiology. *Current Paediatrics*, Vol.16, No.1, (February 2006), pp.70-74, ISSN 0957-5839
- Wasserman, E.; Myara, A.; Lokiec, F.; Goldwasser, F.; Trivin, F.; Mahjoubi, M.; Misset, J.L. & Cvitkovic, E. (1997). Severe CPT-11 toxicity in patients with Gilbert's syndrome: two case reports. *Annals of Oncology*, Vol.8, No.10, (October 1997), pp.1049-1051, ISSN 0923-7534

- Weinshilboum, R.M.; Otterness, D.M. & Szumlanski, C.L. (1999). Methylation pharmacogenetics: catechol O-methyltransferase, thiopurine methyltransferase, and histamine N-methyltransferase. *Annual Review of Pharmacology and Toxicology*, Vol.39, (1999), pp.19–52, ISSN 0362-1642
- Wells, P.G.; Mackenzie, P.I.; Chowdhury, J.R.; Guillemette, C.; Gregory, P.A.; Ishii, Y.; Hansen, A.J.; Kessler, F.K.; Kim, P.M.; Chowdhury, N.R. & Ritter, J.K. (2004). Glucuronidation and the UDP-glucuronosyltransferases in health and disease. *Drug Metabolism and Disposition*, Vol.32, No.3, (March 2004), pp.281–290, ISSN 0090-9556
- Williams, A.C. & Ramsden, D.B. (2005). Autotoxicity, methylation and a road to the prevention of Parkinson's disease. *Journal of Clinical Neuroscience*, Vol.12, No.1, (January 2005), pp.6–11, ISSN 0967-5868
- Wood, T.C.; Salavagionne, O.E.; Mukherjee, B.; Wang, L.; Klumpp, A.F.; Thomae, B.A.; Eckloff, B.W.; Schaid, D.J.; Wieben, E.D. & Weinshilboum RM. (2006). Human arsenic methyltransferase (AS3MT) pharmacogenetics: gene resequencing and functional genomics studies. *The Journal of Biological Chemistry*, Vol.281, No.11, (March 2006), pp.7364–7373, ISSN 0021-9258
- Xie, W.; Yeuh, M.F.; Radomska-Pandya, A.; Saini, S.P.; Negishi, Y.; Bottroff, B.S.; Cabrera, G.Y.; Tukey, R.H. & Evans, R.M. (2003). Control of steroid, heme, and carcinogen metabolism by nuclear pregnane X receptor and constitutive androstane receptor. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.100, No.7, (April 2003), pp.4150–4155, ISSN 0027-8424
- Zhang, J.; Xie, X.Y.; Yang, S.W.; Wang, J. & He, C. (2010). Nicotinamide N-methyltransferase protein expression in renal cell cancer. *Journal of Zhejiang University. Science. B*, Vol.11, No.2, (February 2010), pp.136–143, ISSN 1673-1581
- Zhou, S. (2006) Clinical pharmacogenomics of thiopurine S-methyltransferase. *Current Clinical Pharmacology*, Vol.1, No.1, (January 2006), pp.119–128, ISSN 1574-8847



Topics on Drug Metabolism

Edited by Dr. James Paxton

ISBN 978-953-51-0099-7

Hard cover, 294 pages

Publisher InTech

Published online 22, February, 2012

Published in print edition February, 2012

In order to avoid late-stage drug failure due to factors such as undesirable metabolic instability, toxic metabolites, drug-drug interactions, and polymorphic metabolism, an enormous amount of effort has been expended by both the pharmaceutical industry and academia towards developing more powerful techniques and screening assays to identify the metabolic profiles and enzymes involved in drug metabolism. This book presents some in-depth reviews of selected topics in drug metabolism. Among the key topics covered are: the interplay between drug transport and metabolism in oral bioavailability; the influence of genetic and epigenetic factors on drug metabolism; impact of disease on transport and metabolism; and the use of novel microdosing techniques and novel LC/MS and genomic technologies to predict the metabolic parameters and profiles of potential new drug candidates.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Petra Jančová and Michal Šiller (2012). Phase II Drug Metabolism, Topics on Drug Metabolism, Dr. James Paxton (Ed.), ISBN: 978-953-51-0099-7, InTech, Available from: <http://www.intechopen.com/books/topics-on-drug-metabolism/phase-ii-drug-metabolism>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821