https://doi.org/10.31925/farmacia.2022.4.1 **REVIEW**

MINI-REVIEW ON THE IMPLICATIONS OF GENE POLYMORPHISM IN THE METABOLISM OF XENOBIOTICS

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Abstract

One of the most common medical issues in children and adults is accidental poisonings ranging from medicines to toxic substances such as alcohol and toluene and even metals like iron and lead. The way these substances are metabolised depends on a plethora of factors such as age, sex and even ethnicity. Besides these factors, there is one that holds an even more significant weight on how substances are metabolised - genes, or more precisely, alleles of specific genes. In recent years, genetic studies have significantly increased in number, and more and more genetic polymorphisms are being discovered and studied for their different effects compared to wild types. We performed a literature search on the subject comprising studies focusing on the most common substances in intoxications, as well as polymorphisms of CYP450 isoenzymes, HLA system and others. We obtained various studies on the subject highlighting differences in expression depending on the present allele, with some having diametral opposed effects while others being null. Thorough knowledge of these complex mechanisms is an important first step towards the development of tests to detect susceptibility to severe side effects and towards rapidly customising the therapeutic approach.

Rezumat

Un aspect clinic sensibil, la copii și adulți, este otrăvirea accidentală cu diverse substanțe, de la medicamente la substanțe toxice cum ar fi alcoolul, toluenul sau chiar metale ca fierul și plumbul. Modul în care aceste substanțe sunt metabolizate este dependent de o varietate de factori cum ar fi vârsta, sexul sau etnia. Pe lângă aceștia, factorii genetici își pun amprenta considerabil asupra metabolismului substanțelor, fiind descoperite din ce în ce mai multe polimorfisme genetice. În acest studiu am analizat date din literatura de specialitate care se concentrează pe cele mai comune intoxicații, precum și diferite polimorfisme genetice. Aprofundarea acestor mecanisme complexe reprezintă un prim pas spre dezvoltarea de teste capabile să detecteze susceptibilitatea individuală la diferite substanțe, precum și personalizarea terapiilor.

Keywords: pharmaceutical genetic studies, CYP450 polymorphism, genetic variants, metabolism of medical agents, genetic implications in metabolism

Introduction

Over the years, more and more studies show that most accidental poisoning events occur in adults and only a relatively small percentage in children or young adults under the age of 20. Young children (around 1 year of age) have the highest risk of fatal poisoning through ingestion of the toxic agent in most cases. On the other hand, compared to young children, adolescents are more likely to be intoxicated with alcohol or illicit drugs. Males are more frequently intoxicated than females, possibly due to social behaviour stigma associated with gender [1].

The most commonly ingested agents are medicines - analgesics, antipyretics, anticonvulsants, antidepressants, vitamins, etc. (52% of cases), followed by non-medicinal substances (cosmetics, personal care products, plants, cleaning products, pesticides, hydrocarbons, etc.) found in the environment. In the case of children, the frequently lethal agents ingested are anticonvulsants, antidepressants, cleaning products and hydrocarbons [1].

With ageing and development, the expression pattern of the genes involved in the metabolism of medicines/ toxic agents changes [2].

Many genetic polymorphisms of CYP 450 isoenzymes and other enzymes involved in medicine metabolism (glutathione S-transferase, N-acetyltransferase 2, UDP-glucuronyl-transferase B7) have been associated with drug-induced liver injury (DILI). Genetic polymorphism continue to be associated with modifications in the pharmacokinetics and pharmacodynamics of multiple drugs affecting the body response to the

treatment [3]. The polymorphism of hepatobiliary transporters (BSEP - bile salt export pump, MDR3 - multidrug resistance 3) may lead to drug-induced cholestasis at low medicine doses [4].

The genetic polymorphism of cytochrome P450 isoenzymes may decrease the metabolism of the toxic agent/ medicine, lead to a lack of metabolism or even trigger its fast metabolism. [5] Some of the main members of the CYP450 isoenzymes involved in substances metabolism and their activity are illustrated in Table I.

Chronic alcohol ingestion, which is often accidental in children, enhances the activity of the CYP2E1 and CYP4A isoenzymes, an effect that lasts about 10 days after ingestion. Alcohol also accelerates glutathione turnover by impeding the mitochondrial transport of glutathione. Medicines such as acetaminophen (paracetamol), isoniazid, methotrexate, vitamin A, or drugs like cocaine have higher hepatotoxicity rates when associated with alcohol ingestion [5, 6].

CYP2D6 fast and ultra-fast metabolisers are faster in experiencing the side effects of codeine or tramadol (opioid analgesic) poisoning [7, 8]. Tricyclic antidepressants are converted to active metabolites *via* CYP2C19, and CYP2D6 is required for the inactivation and elimination of the active drug. Slow CYP2D6 metabolisers are more prone to rapidly developing side effects with antidepressant poisoning (amitriptyline, nortriptyline, venlafaxine, fluoxetine, etc.) [8].

Other medicines, such as diazepam, are metabolised *via* CYP2C19 and CYP3A4 to the active metabolite desmethyldiazepam. The CYP2C19*17 allele is associated with ultra-fast metabolic status, with a lower risk of developing side effects during accidental poisoning. The wild-type CYP2C19*1 allele (an enzyme with normal activity) is associated with a risk equal to that in the general population of developing side effects in case of poisoning. The CYP2C19*3 allele, which contains c.636G>A in exon 4 with the occurrence of a premature stop codon, leads to a slow metabolic status, with a high risk of rapidly developing side effects to diazepam. Ingestion of Brussels sprouts, cabbage, cruciferous vegetables (broccoli), high-protein diet induces the expression of cytochrome P450, especially CYP1A2. On the other hand, consumption of grapefruit juice, a low-protein diet or severe malnutrition inhibits CYP3A and interacts with the metabolism of some medicines [9-11].

Another factor that influences the body's response to medicine metabolism is the polymorphism of the HLA system. Some HLA haplotypes favour the side effects of medicines.

For instance, HLA-DR6 is associated with toxic hepatitis caused by chlorpromazine, HLA-A11 with hepatitis associated with tricyclic antidepressants, HLA DRB1*5701 with an 80-fold higher risk of flucloxacillin hepatotoxicity compared to the general population. SNPs in the HLA-DRB1*1501 - DQB1*0602 alleles are also associated with hepatotoxicity and toluene-diisocyanate-induced asthma, while DRB1*1501 - DQB1*0602 is associated with cholestasis upon amoxicillin-clavulanic acid administration [5].

Some studies reveal the importance of ontogeny in the development of pharmacogenetic pathways, of the enzymes involved in medicine metabolism, drug carriers and drug targets [16, 17]. The pharmacokinetics of a medicine is of utmost importance in providing and maintaining the desired therapeutic effect with the drug delivery systems being key players [18]. For instance, the interaction of simvastatin, one of the most widely used treatments in hypercholesterolemia, with the product of the SLCO1B1 gene encoding an OATP1B1 anionic protein transporter with a role in drug distribution. Adults with the rs4149056 variant of the SLCO1B1 gene have high drug plasma concentrations and are at higher risk of rhabdomyolysis and myopathy [19]. In children, simvastatin or pravastatin are rarely prescribed, especially in case of family hypercholesterolemia or after transplantation, but it may be accidentally ingested by children at home [20].

In addition to the unclear impact of SLCO1B1 variants on the risk of myopathy in children, another problem is the optimal age of use of HMG-CoA reductase inhibitors, which is over 10 years of age in boys and after the onset of puberty in girls. Early therapeutic or accidental exposure may affect sexual maturation, especially in girls [21].

Materials and Methods

We performed an initial literature search in September 2020 in order to assess the current progress in terms of drug metabolism dependent on gene variants. Three main databases were used: google scholar, medline and hindawi. The search was performed using different combinations of the keywords such as: drug metabolism, CYP450 polymorphisms, genetic factors involved in drug metabolism etc. and articles were selected based on their relevance, their time of publication and whether or not we considered their subject approach linked to ours. We excluded articles on not so common toxic substances or studies that have not been researched enough in order to be considered established.

Results and Discussion

Metabolism of most common ingested substances

Acetylsalicylic acid (AAS, aspirin)

When delivered in therapeutic doses, aspirin normally acts by irreversibly inhibiting cyclooxygenase-1 (COX-1) by acetylating serine residues at position 529. COX-1 catalyses the conversion of arachidonic acid to prostaglandin G2 and H2, which are then converted by

thromboxane-synthetase to thromboxane A2 (TXA2) with vasoconstrictor activity and platelet aggregation [22].

Haemolytic anaemia is reported in patients with glucose 6-phosphate-dehydrogenase deficiency in acute aspirin poisoning [23]. In the asthmatic population, individuals with specific polymorphisms have been reported to be more susceptible to bronchoconstriction following aspirin ingestion and aspirin-induced asthma (AIA). Several studies in the Polish and Korean populations have reported an association between HLA*DPBI*0301 and a higher prevalence of rhinosinusitis and nasal polyps; therefore, this specific allele can be considered a robust genetic marker for identifying AIA phenotype [24]. Another study has reported a significant association between CYP2C9-118T>C(gene that is involved in the hydroxylation and glucuronidation of aspirin) allele and aspirin-induced urticaria (AIU), suggesting that this allele may contribute to the developing of AIU phenotype[25].

Table I

Main isoenzymes from the P450 family that are involved in the metabolism of different medical and non-medical substances. *PAHS – polycyclic aromatic hydrocarbons, *ALL – acute lymphoblastic leukaemia; *rs762551 – encodes 1A2*1F; *NSAIDs – non-steroidal anti-inflammatory drugs, *ARBs – angiotensin II receptor blockers (after genecards)

Family	Member	Expression	Associations	Allele/Polymorphisms	Function
1A	1A1	Expression is induced by some PAHs, some of which are found in cigarette smoke	Lung cancer risk	*CYP1A1*2A, CYP1A1*2C, CYP1A1*3* and *CYP1A1*4* polymorphisms - associated with different cancers (breast, colon, ovary, lung, oral cavity carcinoma and ALL [12])	-metabolise some PAHs to carcinogenic intermediates
	1A2	-endogenous substrate unknown -xenobiotic substrate: caffeine, aflatoxin B1, acetaminophen.	Porphyria Cutanea Tarda and Acetaminophen Metabolism	Higher enzyme activity was observed among those who were homozygous or heterozygous for the -163C>A polymorphism (rs762551)*, and this was more pronounced among smokers [13]	-metabolism of various endogenous substrates, including fatty acids, steroid hormones and vitamins
2C	2C9	expression is induced by rifampin, warfarin	Coumarin Resistance, Diaphragm Disease	*2, *3, *5, *8, *11, *12, *13 decreased *6, *15 no function [14]	-metabolism of NSAIDs, oral antidiabetic agents, and (ARBs; involved in the disposition of warfarin
	2C19	antidepressants	Deficiencies of CYP2C19 lead to benzodiazepine poisoning, Cyp2c19-related poor drug metabolism, peptic ulcer disease	*1 - does not discriminate between accidental poisoning and intentional can lead to side effects development *3 - slow metabolic status, high risk of rapidly developing side effects to diazepam *17 - ultra-fast metabolic status, decreased risk of developing side effects	Converts tricyclic antidepressant to active metabolites (e.g. together with CYP3A4 converts diazepam to desmethyldiazepam)
2D	2D6	antidepressants, antipsychotics, analgesics and antitussives, beta-adrenergic blocking agents, antiarrhythmics and antiemetics	Cyp2d6-related poor drug metabolism, neuroleptic malignant syndrome	Highly polymorphic *2a - 2x2 gene duplication, ultrafast metaboliser of codeine *3, *4, *5, *6, *7, *8 - poor function *10, *41 - medium metabolizer	Eliminates active drugs (e.g. Eliminates the active metabolite obtained via CYP2C19)
3A	3A4	Grapefruits, low protein diet or severe malnutrition inhibits expression	reduces codeine clearance and increases its toxic effects, acetaminophen metabolism and drug allergy	The majority of genetic polymorphisms to the CYP3A4 gene result in decreased function of the enzyme activity [15, 16]	metabolism of approximately half the drugs in use today, including acetaminophen, codeine, cyclosporin A, diazepam, erythromycin, some steroids and carcinogens.

Diclofenac

The active substance diclofenac is a non-steroidal anti-inflammatory drug with a functional carboxylic acid group. Diclofenac metabolism is accomplished primarily by uridine-5'-diphosphoglucuronosyl transferase 2B7, followed by cytochrome P450 (CYP2C9 and 3A4). Mutations in CYP2C9 (Arg97, Phe114, Asn289 and Ser286) influence the affinity and specificity

of the substrate. Several studies have concluded that the most common symptoms of diclofenac side-effects (gastrointestinal bleeding and hepatoxicity) are indeed associated with CYP2C8*3 and CYP2C9*2*3 by reducing its metabolism [26-28], and another study illustrated that NSAIDs biotransformation by CYP2C9 is different based on gender [29]. The toxicity of diclofenac is due to its metabolite acyl-glucuronide-diclofenac, a metabolite capable of forming covalent bonds with liver proteins. Intrahepatic transport of the metabolite depends on the activity of the multi-drug-resistance-protein 2 (MDRP 2) intrahepatic canalicular transporter. People with mutations of this protein may develop hepatic toxicity at therapeutic or low diclofenac doses ingested accidentally [30]. The UDP-Glucuronosyltransferase-2B7 gene variant UGT2B7*2, commonly present in liver injuries determined by diclofenac, has been shown to determine a 35% reduced activity of diclofenac acyl glucuronide hydroxylation [31].

Opioids and agonists (codeine, dextromethorphan, diphenoxylate - Lomotil®, fentanyl, hydrocodone, hydromorphone, loperamide, meperidine, methadone, morphine, oxycodone, paregoric, propoxyphene and tramadol).

Opioids and agonists are differently metabolised from one individual to another, based on each individual's genetic polymorphism. Most opioids are metabolised by cytochrome P450. The pharmacological action of opioids is mediated by G protein-bound opioid receptors located in the brain and spinal cord. Three receptor subtypes were cloned: mu-opioid receptor (μ), kappa-opioid receptor (κ) and delta-opioid receptor (δ). The most frequently prescribed opioid derivatives act on the mu-opioid receptor, and the genetic polymorphism of the receptor is involved in opioid response variation. More than 100 polymorphisms have been described in the gene of this OPRM1 receptor, the most studied being OPMR1 A118G found in 2 - 48% of the human population (depending on ethnicity). OPRM1 polymorphism rs1799971 has been associated with increased response to codeine and tramadol but decreased to morphine, fentanyl and sufentanil [15, 32].

P-glycoprotein (P-gp) is primarily a drug efflux molecule which, in the case of opioids, is responsible for their concentrations at their target sites. ATP-Binding Cassette subfamily B member 1 (ABCB1) encodes this protein, and its polymorphisms have been associated with altered responses to various opioids. For example, the variant rs1045642 has been linked to decreased response to morphine and fentanyl, whereas this variant and rs1128503 increased the risk of central nervous system depression in breastfeeding infants [33].

Dextromethorphan is a common ingredient found in antitussives, used to temporarily relieve cough caused by the common cold. The active metabolite (dextrorphan) is a noncompetitive antagonist for the N-methyl-D-aspartate receptor, which, in the fast metabolisers P450 2D6, has been reported to be linked with psychotic manifestations [34]. As observed in Table I, patients with ultra-rapid metabolisers of CYP2D6(*1/*1xN, *1/*2xN/xN) are more prone to the side effects of codeine. At the same time, the variants *1/*2xN and *2/*2xN have been associated with increased opioid-related side effects, whereas the allele *17/*17 and *36/*36 with decreased response to codeine. Another CYP family member associated with the metabolism of opioids is CYP2D6*4/*4 which determines a reduced response to tramadol[15, 33].

Cases have been reported in which the mother was an ultra-fast metaboliser of codeine and the infant rapidly developed signs of morphine poisoning. Madadi *et al.*, 2007 reported the case of an infant who died at the age of 13 days after being breastfed. The mother had received codeine as a postpartum analgesic. Analysis of breast milk showed a morphine level 4 times higher than expected, which led to genetic testing. The mother was heterozygous for the CYP2D6∗2A allele and had CYP2D6∗2x2 gene duplication. With three functional alleles, the mother was an ultra-fast codeine metaboliser, which had led to high metabolite (morphine) concentrations in her blood and breast milk [35, 36].

CYP2C19 gene polymorphism is involved in the metabolism of diazepam, etizolam, quazepam and desmethylclobazam, while CYP3A5 is involved in the metabolism of alprazolam and midazolam. Thus, CYP2C19 enzyme deficiencies quickly lead to side effects or benzodiazepine poisoning [37].

Acetaminophen

Due to its frequent use as an analgesic or antipyretic, acetaminophen is common in paediatric poisonings and is the most common cause of acute liver failure in the USA. Some authors report lower hepatotoxicity in children after one overdose, the toxic dose being 200 mg/kg body weight.

Acetaminophen is metabolised by the liver in several ways: glucuronidation (a reaction catalysed by UDP-glucuronosyltransferase of UGT1A1 and 1A6), sulfation (catalysed by sulfotransferases SULT1A1, 1A3/4, and 1E1), oxidation, hydroxylation and de-acetylation. Other enzymes are also involved in these reactions: CYP2E1 and cytochrome P450. The metabolites from these reactions lead to glutathione depletion in the liver and alter some cellular proteins. In terms of metabolism, interethnic and interpersonal differences have been reported [38].

Patients with Gilbert's syndrome or Crigler-Najjar syndrome (UGT1A1 mutations) experience the toxic effects of acetaminophen at lower doses compared to the general population [39-41]. A study conducted by Court. and his team has observed that the single-nucleotide polymorphism UGT2B15*2/*2 exhibited

a lower acetaminophen clearance compared to their *1/*1 counterparts [42] and, in general, might be a slower metaboliser of acetaminophen, resulting in increased risk for liver damage and oxidative metabolism to N-acetyl-β-benzoquinone (NAPQI) - the metabolism with the highest toxicity [43].

Mice with hepatic steatosis have recently been shown to have increased UDP-glucuronosyltransferase gene expression compared to healthy mice. Hepatic steatosis appears to attenuate acetaminophen-induced hepatotoxicity by inhibiting CYP2E1 induction [44].

About 25 - 35% of the acetaminophen entering the bloodstream is recovered by acetaminophen sulfate. Patients with mutations in the NAS1 gene encoding a renal transporter involved in the reabsorption of SO4-2 inorganic sulfate are more likely to develop hepatotoxicity to acetaminophen [45].

SULT genes encoding sulfotransferases are also involved in acetaminophen sulfation. A significant increase in SULT1A1 gene expression in the liver of patients with steatosis and increased sulphation activity of the medicine have been reported [46], while the variant SULT1A1*2/*2 has been associated with lower acetaminophen clearance [42, 47]

Cytochrome P450

After a therapeutic dose is delivered, 5 - 15% acetaminophen is excreted in urine as mercapturic acid or bound to cysteine. CYP2E1*1 variant has been associated with significantly reduced oxidation clearance [42], whereas homozygous carriers of the T allele variant of the same gene exhibited an increase in the elimination rate of acetaminophen compared with CC and CT individuals [43]

Iron toxicity

Iron poisonings are quite common in paediatric practice due to the accessibility of treatments with iron preparations and the attractive form of iron preparations for children (syrups, tablets that resemble candy, etc.). Iron exerts both local and systemic effects, being toxic to mitochondria. Severe and low-iron poisoning may occur in children with haemochromatosis [48].

Hemochromatosis is a genetic disease due to homozygous mutations (specifically C282Y mutation) in HFE (which is an HLA class 1 molecule), or non-HFE forms determined by mutations in hepcidin antimicrobial peptide gene (HAMP), hemojuvelin (HJV) and transferrin receptor 2 (T2F2) characterised by a systemic iron overload of genetic origin caused by a reduction in the concentration of the iron regulatory hormone hepcidin-ferroportin binding. Gene C282Y has an autosomal recessive inheritance, and even if its homozygous form has a high prevalence, but only in a few cases will it accumulate enough to cause damage. Missense mutations in HAMP and solute-carrier family 40 member 1 (SLC40A1 - gene providing instruction for making ferroportin) have been linked to loss of hepcidin activity, whereas the heterozygous mutations in SLC40A1 might lead to systemic iron overload, called ferroportin disease. The loss of TfR2 and HJV or ferroportin mutations trigger gull-blown hemochromatosis [49-51].

This phenomenon is accounted for by two mechanisms: i) the HFE gene product binds to the transferrin receptor, decreasing the latter's ability to bind transferrin and thus decreasing intestinal iron absorption; patients with hemochromatosis have a low amount of HFE protein, which will lead to overexpression of the transferrin receptor and then to increased iron absorption even in deficient individuals; ii) HFE protein deficiency in patients with hemochromatosis leads to increased intestinal expression of DMT-1 protein (bivalent metal transporter), which leads to higher Pb absorption [52, 53].

Severe iron deficiency has been observed in patients with TMPRSS6 mutations due to increased plasma levels of hepcidin characterised by severe anaemia and resistance to iron supplementation [50, 54].

Valproic acid (VPA)

VPA is a saturated, single-stranded fatty acid derived from the natural product valeric acid, which differs in structure from all other anticonvulsants with a cyclic structure. It is used as an antiepileptic and anticonvulsant and also for the treatment of migraines, bipolar disorder, anxiety and mental illnesses. It is currently used as adjuvant therapy in oncology, HIV infections and neurodegenerative diseases due to its ability to inhibit histone deacetylation [55-57]. Valproic acid is metabolized at the hepatic level into several metabolites and an overdose may lead to hyperammonaemia [58].

In recent years, it has been suggested that genetic deficiencies might be the underlying mechanisms behind valproic acid hepatotoxicity, deficiencies in antioxidant enzymes such as glutathione S-transferases (GSTs), catalase, superoxide-dismutase and glutathione-peroxidase included. A study conducted by Linfeng Ma and his team on the Chinese population with epilepsy has illustrated that carriers of CAT C-262T have an increased risk of developing abnormal liver function [59].

In the past has been reported that resistance to antiepileptic drugs through calcium channels blockade is associated with single nucleotide polymorphisms, such as the functional polymorphism rs3812718 of the SCN1A linked to resistance in children [60]. Another study suggested an association between UGT1A6 552A>C, high VPA plasma levels and symptoms such as ataxia, liver damage, tremor, hallucinations [61-63]. Increased VPA levels have also been observed and associated with polymorphisms of the CYP family, for example, CYP2A6*1/*4, CYP2A6*4/*4, CYP2B6*6 and CYP2C9*3 [64].

An interesting aspect has been observed in the case of UGT2B7 G211T and C161T polymorphisms. They have exhibited the ability to affect the pharmaco-

kinetics of valproic acid in epilepsy patients, which further suggests that in their case, the dose of VPA might need to be increased or decreased in order to fulfil its therapeutic effect [65]

Polymerase-gamma genes (POLGs), a nuclear gene with a role in mitochondrial metabolism, are also associated with increased toxic effects of valproic acid. Mutations in the POLG gene lead to Alpers - Huttenlocher syndrome, with an increased risk of hepatotoxicity when valproic acid is ingested. POLG polymorphism, present in 5% of the population, is also correlated with migraine, epilepsy, and Parkinson's disease, for which valproic acid is prescribed, with a risk of rapid onset of toxic effects [66, 67].

Other genetic polymorphisms in the X-Box Binding Protein 1 (XBP1) gene encoding a transcription-promoting factor may be associated with a higher risk of side effects due to valproic acid ingestion. The G rs226957 (116C> G) allele is associated with increased valproic acid response in patients with bipolar disorder or in those who accidentally ingest the drug [68].

Hyperhomocysteinemia due to MTHFR 677C/T gene mutation (5 - 22% of the population) may be a risk factor for thromboembolic events, exacerbated by valproic acid ingestion [57, 69].

Ethanol

Ethanol poisoning is often accidental in young children and sometimes voluntary in older children. Ethanol is the most common toxic agent: it is easily accessible to children, it exists in almost any home, and it may be ingested by imitating the behaviour of adults.

Two enzymes play a major role in alcohol metabolism: alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), both with multiple isoforms (isoenzymes) with slow or rapid metabolic action. The dose at which alcohol becomes toxic and also the dose at which side effects occur due to sensitivity to alcohol are both dependent on this action.

ADH genes are located on chromosome 4q21, spanning on 370kb. The ADH gene family comprises over 20 isoenzymes that differ in the type of alcohol they metabolise (ethanol, retinol, aliphatic alcohols, hydroxysteroids or lipid peroxidation products), as well as in the ethanol metabolism rate [70].

The polymorphism of the ADH1B gene leads to the emergence of isoenzymes with a higher rate of alcohol metabolism (and side effects of poisoning due to higher doses of alcohol). Carriers of allele ADH1B*2 (heterozygous or homozygous), ADH1B*3 and ADH1C*1, have more intense enzymatic activity and, therefore, a higher rate of alcohol metabolism compared to ADH1B*1 homozygotes. The ADH1B*3 allele occurs almost exclusively in the African, African American and some Native American populations and has an extremely low frequency in other populations [70-72].

While ADH2 expression is almost exclusively hepatic, recent studies have suggested that ADH3 contributes to the first stage of alcohol metabolism in the stomach. People who express ADH3 genes have increased and rapid absorption of ethanol from the digestive tract [73].

On the other hand, ALDH2*2 polymorphism leads to an enzymatic form with low activity and, therefore, to the occurrence of side effects of alcohol intoxication at lower doses. For example, Asians often experience facial flush after drinking alcohol compared to Caucasians. This is due to the absence in the Asian population of the ALDH1 isoenzyme with a role in lowering serum acetaldehyde resulting from hepatic metabolism of alcohol [74]. Homozygous variant ALDH2*2 has been associated with full protection against developing alcohol dependence by intense, unpleasant side effects of alcohol intoxication, and its presence or inactivation often results in hypertension risk [75], whereas partial protection by ALDH*1/*2 can be attributed to a faster elimination of acetaldehyde [76].

Recent studies have suggested an association between polymorphism of the human brain-derived neurotrophic factor (BDNF) gene, val66met, and the severity of foetal alcohol spectrum disorders, which can at least illustrate a potential novel genetic risk factor [77].

The study conducted by London *et al.* on the effects of TaqIA polymorphism on ethanol response in the brain has illustrated that the A1 allele on the ANKK1 might be linked to lower dopaminergic metabolism and higher alcoholism risk [78].

Toluene

Accidental exposure to and poisoning with toluene is rare. About 25 - 40% of toluene is excreted through the lungs, the remainder being excreted as benzyl alcohol after its metabolism by the cytochrome P450 enzymes. Five CYP enzymes involved in toluene metabolism are described: CYP 1A2, CYP 2B6, CYP 2E1, CYP 2C8 and CYP1A1. Benzyl alcohol is also metabolised to benzaldehyde rather by the CYP P450 system than alcohol dehydrogenase. Benzaldehyde is metabolised to benzoic acid rather by aldehyde dehydrogenase-2 (ADH-2) than by ALDH-1 [79].

Exposure to toluene may be simultaneous with exposure to cigarette smoke or alcohol ingestion. Wallen, M *et al.* pointed out that acute alcohol consumption may significantly decrease toluene excretion and thus increase its toxicity [80]. Chronic alcohol consumption, rare in children, increases toluene metabolism by CYP2E1 induction. Exposure to cigarette smoke or active smoking increases toluene removal also by enzymatic induction. A low-carbohydrate diet and fasting also lead to enzymatic CYP 2E1 induction and increase toluene metabolism, while a low-protein diet may decrease CYP P450

activity, thus reducing toluene excretion [81,82]. CYPE1 has the ability to produce reactive oxidative species, therefore, triggering oxidative stress as a consequence of toluene exposure. Nephrotoxic effects of toluene have also been associated with null GSTT1 or null GSTT1/GSTM1[83].

Lead

Children's habit of hand-to-mouth and their higher respiratory rate and intestinal absorption make children more prone to lead (Pb) poisoning compared to adults [84], Pb being found in drinking water, dietary supplements, paints, leaded gasoline and even ceramic products [4,85] and even soil as a consequence of improper discarding of batteries, lead paints, fuels and even plumbing materials [86]. Lead poisoning is especially dangerous during pregnancy in high polluted areas (e.g. near landfills or heavily industrialized areas) as it increases the chances of birth defects and still births [87].

At least three genes have been described as being involved in the bioaccumulation and toxicity of lead Pb in humans.

δ-Aminolevulinic Acid Dehydratase (ALAD) is an enzyme involved in heme biosynthesis. 2 alleles have been described that determine three isoenzymes (1-1, 1-2, 2-2) involved in porphobilinogen synthesis [88] Some studies have shown that the ALAD2 isoform has a higher affinity for Pb [89]. Hence the ALAD 1-2 and 2-2 isoforms are considered genotypes with a higher risk of developing toxic effects upon exposure to elevated levels [90], and those carrying 1-2 genotype have been observed to have a higher blood lead level compared to 1-1 [91]

The T allele in the rs1805313 locus of the ALAD gene is correlated with low Pb levels in individuals exposed to the toxic agent, while heterozygotes for the rs2228083 locus and C allele carriers in the rs1139488 locus are at higher risk of poisoning at lower exposures. Vitamin D receptor gene polymorphism also appears to play a role in Pb poisoning [52, 92].

There are also studies that report ALAD enzyme inhibition by exposure to cigarette smoke and alcohol consumption [93].

Conclusions

In conclusion, genetic polymorphisms can alter the effects of individual exposure to toxic agents. Thorough knowledge of these complex mechanisms could lead to the development of tests to detect susceptibility to severe effects of toxic agents and to rapid and customised therapeutic approaches. Improving preventive actions aimed at protecting the most vulnerable subjects, children, can be an important goal in the near future.

Conflict of interest

The authors declare no conflict of interest.

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