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Glucuronidation enzymes, genes and psychiatry

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Abstract

The phase I cytochrome P450 (CYP) isoenzymes have received substantial attention in the pharmacogenetic literature. Researchers are beginning to examine the role of the phase II UDP-glucuronosyltransferase (UGT) enzymes, which produce products that are more water-soluble, less toxic and more readily excreted than the parent compounds. Several reasons may have contributed to neglect of UGTs (compared to CYPs) including: (1) the overlapping activity of UGTs and lack of selective probes; (2) the complexity of the glucuronidation cycle; and (3) the difficulty in developing analytic methods to measure glucuronides. Current CYP knowledge is used as a model to predict advances in UGT knowledge. At least 24 different UGT human genes have been identified and are classified in two families (UGT1 and UGT2) based on sequence homology. The UGT1A subfamily (genes located on chromosome 2) glucuronidates bilirubin, thyroid hormones, and some medications. UGT1A4 metabolizes tricyclic antidepressants and some anti-psychotics. The UGT2B subfamily (genes located on chromosome 6) glucuronidates sexual steroids and bile acids. Oxazepam and lorazepam are mainly metabolized by glucuronidation. Anti-epileptics with mood-stabilizing properties are frequently metabolized by UGTs. Opioid and nicotine addiction may also be influenced by glucuronidation. Glucuronidation of serotonin may be important during fetal development. UGTs appear to be in small concentrations in brain tissue (and higher concentrations at brain capillaries). However, UGTs may be localized in certain brain areas to provide a neuroprotective function. This review illustrates the importance of glucuronidation and the implications for psychiatry.

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Introduction

The Human Genome Project is providing a myriad of new genes influencing brain function. The function of these genes will need to be determined once the sequence is known. Current knowledge of genes influencing brain function is limited, and most mental illness appears to be complex and influenced by many genes and possibly numerous environmental factors. The study of genes, which control the systems associated with psychopharmacological treatments, appears to be a good starting point. One can focus on genes controlling neurotransmission (pharmacodynamics) or on genes involved in controlling pharmacokinetic factors (absorption, distribution, metabolism and elimination of drugs). The pharmacogenetic

literature has focused on genes that mediate pharmacokinetics (Alvan et al., 2001; Kirchheiner et al., 2001) and more recently, genes influencing pharmacodynamics have been investigated. However, the psychiatric literature, particularly in schizophrenia (Cichon et al., 2000; Kawanishi et al., 2000; Malhotra, 2001; Rietschel et al., 1999) has mainly focused on genes that mediate pharmacodynamics while neglecting those that influence pharmacokinetics.

It is very probable that variations in genes affecting drug handling make substantial contributions to the wide interpatient variability in response to drug therapy often seen in psychiatric patients or to drug addictions. Advances in pharmacogenetics may not be a magic answer for psychopharmacotherapy improvements. Psychiatric disorder complexities and poor compliance of psychiatric patients contribute to the difficulty of treating psychiatric patients. Some cases of poor compliance may be explained by adverse drug reactions associated with polymorphic variations.

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The metabolic enzymes are traditionally divided into two categories, phase I (oxidation, reduction, or hydrolysis) and phase II (conjugation) enzymes (Bertz and Granneman, 1997; Shen, 1997). Glucuronidation enzymes are the most important group of the phase II enzymes and are the focus of this review. UDP-glucuronosyltransferase (UGT) enzymes produce products that are more water-soluble, usually less biologically active, and more readily excreted than the parent compounds. The glucuronides can be excreted by renal and biliary elimination. The glucuronides eliminated by the biliar system can be reabsorbed using the enterohepatic cycle.

The cytochrome P450 (CYP) isoenzymes are the most important group of enzymes of phase I reactions (Rendic and Di Carlo, 1997; Touw, 1997). Compared to CYP, the UGTs have been neglected by researchers. Several reasons may have contributed to this neglect, including: (1) the UGT system includes many enzymes whose activity overlaps, and in contrast with CYPs, there are few selective probes; (2) the complexity of the glucuronidation cycle, that may include in-vivo deconjugation by β -glucuronidase and reabsorption in the enterohepatic cycle; and (3) glucuronide analyses represents a serious challenge, since more sophisticated methods such as liquid chromatography-mass spectrometry (LC-MS) or radiochemical high-performance liquid chromatography (HPLC) (Ethell et al., 1998) are needed, and frequently analytical standards are missing since pure conjugated products are unavailable (Hawes, 1998). It is difficult to synthesize glucuronidation products, particularly *N*-glucuronides, and frequently there are no commercial sources (Hawes, 1998). It is easier to establish glucuronide concentrations by indirect analysis (Hawes, 1998). First, the concentration of the parent compound is established, then the parent compound glucuronide is hydrolysed (by chemical or enzymic hydrolysis) leading to an increase of the parent compound. Therefore, the glucuronide concentration is calculated by subtracting the concentration of the parent compound before hydrolysis from the concentration of the parent compound after hydrolysis.

Better knowledge of CYP and UGTs will surely explain some psychopharmacological treatment failures, drug intoxications and adverse drug events. Knowledge of a patient's genome, including those genes of metabolic enzymes, will greatly facilitate the selection of individualized psychopharmacological treatments. With the new advances in technology, this may be highly plausible in the near future. The journal *Science* (Editorial comment, 1997) stressed the importance of this approach by naming 'personalized prescriptions'

as one of the six research horizons for 1998. In 1999, the lay journal *Time* predicted that by 2015, GeneChips will be used to tailor medications to each patient's genes and prevent adverse drug reactions (Lertola, 1999). In effect, the development and marketing of new technologies such as GeneChips (Flockhart and Webb, 1998; Watson and Akil, 1999) will permit simultaneous testing of multiple genes ensuring that pharmacogenetical testing will be a cost-effective tool for clinicians (Wedlund and de Leon, 2001). The consequences of genetic polymorphism are more pronounced when a given pharmacological substrate has a narrow therapeutic range or when the genetic defect causes a complete lack of enzyme activity (e.g. CYP2D6). In fact in 2003, the CYP2D6 GeneChip may be presented to the US Food and Drug Administration (FDA) in order to get approval for marketing. UGT genotyping with new techniques, such as the GeneChip, may be very helpful but other issues (such as enzymic overlap, influence of the enterohepatic cycle, and lack of development of analytic methods to measure glucuronides) may affect its practical use. To date, the consequences of genetic polymorphism for UGTs has been definitely established only for bilirubin (de Wildt et al., 1999) and for a metabolite of irinotecan, an anti-neoplastic drug (Iyer et al., 2002).

The example of CYP

A parallel exists between current knowledge of the UGT gene family and the knowledge of the CYP gene family 10 years ago. Since data on the significance of glucuronidation is limited, one could examine the CYP system as a model to illustrate potential clinical implications. The CYPs are a superfamily of enzymes (Touw, 1997). Many CYPs are essential for life since they are involved in the formation and/or metabolism of critical endogenous compounds (Rendic and Di Carlo, 1997). The CYPs from the first three families are located in the endoplasmic reticulum and appear to be involved in the phase I metabolism of xenobiotic compounds. Each species has its own CYP family. The current theory suggests these enzymes evolved to metabolize chemicals produced by plants. An animal-plant warfare exists where the CYP enzymes in each species have evolved to facilitate the elimination of toxicants most likely found in their foods. Humans use the same CYPs to destroy medications (many derived from plants) that have evolved over many generations as protectants against plant toxicants.

The CYP2D6 isozyme metabolizes many anti-psychotic and antidepressant drugs. The gene that

encodes this enzyme is located on chromosome 22. The CYP2D6 enzyme is expressed constitutively in several tissues so enzyme activity is defined primarily by the type of CYP2D6 alleles expressed in a subject. The only significant environmental factor that may modify the phenotype is the intake of potent inhibitors such as quinidine, paroxetine, or fluoxetine. Therefore, it would seem reasonable for psychiatric researchers and psychiatrists to examine variations in this gene to assess how it may influence response to antipsychotic and antidepressant medications. There is an increasing number of studies on the association of CYP2D6 allelic variations with therapeutic or toxic effects after psychopharmacological treatments for both antipsychotics (Armstrong et al., 1997; Arthur et al., 1995; Iwahashi, 1994; Pollock et al., 1995) and antidepressants (Bertilsson et al., 1981, 1985; Bork et al., 1999; Chen et al., 1986; Krau et al., 1996/1997; Meyer et al., 1998; Spina et al., 1997). Guidelines for antidepressant dosing according to the CYP2D6 genotype have been developed (Kirchheiner et al., 2001). One study has shown that extremes (associated with a lack of activity or abnormally high activity) of the CYP2D6 genotype may be associated with a greater incidence of side-effects (de Leon et al., 1998) and higher treatment costs by extending the length of hospitalizations (Chou et al., 2000). Other more recent pharmacogenetical studies in psychiatry combined genotyping of other CYPs and dopamine receptors (Ozdemir et al., 2001; Segman et al., 2002).

A more interesting finding for most psychiatrists and psychiatric researchers is the role of CYP2D6 on brain function. CYP2D6 is found in some brain areas and may play an important role in protecting certain susceptible brain regions from toxicants that gain access to the CNS. The enzyme appears to be distributed close to areas rich in the dopamine transporter. Some earlier studies suggested that the CYP2D6 genotype may influence the development of Parkinson's disease. For instance, poor CYP2D6 metabolizers (individuals who lack CYP2D6) may be more prone to develop Parkinson's disease (Tanner, 1991). A more recent meta-analysis suggested that the median odds ratio for poor CYP2D6 metabolizers in Parkinson's disease was 1.32 (95% confidence interval 0.98–1.78), indicating that being a poor metabolizer may slightly increase the risk of Parkinson's disease, but this was of borderline statistical significance (Rostami-Hodjegan et al., 1998). The CYP2D6 genotype may also be associated with Lewy body dementia (Saitoh et al., 1995), probably related to Parkinson's disease. However, it does not appear to be associated with Alzheimer's disease (Cervilla et al., 1999).

UGT

Ten years ago knowledge of the UGT enzymes in psychiatry could be summarized as follows: the UGTs are a group of liver enzymes that metabolize some psychiatric medications. At that time the knowledge on genetic disorders of UGTs was limited to two diseases with patronymic names associated with hyperbilirubinaemia due to inherited deficiencies in the UGTs (Crigler–Najjar syndrome and Gilbert's syndrome). The Crigler–Najjar syndrome is a rare familial form, frequently lethal, of severe unconjugated hyperbilirubinaemia caused by an absence of bilirubin conjugation. Gilbert's syndrome is a familial hyperbilirubinaemia characterized by a mild unconjugated hyperbilirubinaemia that is estimated to be found in 5% of the Caucasian population. The formation of bilirubin diglucuronide is decreased and the level of bilirubin monoglucuronide is increased (Burchell et al., 2000).

Our current knowledge in this area is somewhat more extensive. It has been suggested that UGTs may influence carcinogenesis and autoimmunity (Tukey and Strassburg, 2000). This review tries to suggest the possibility that advances in this area may have some significant implications for psychiatry and psychiatric research. Moreover, the role of UGTs is not confined to hepatic metabolism. The olfactory epithelia express a specific UGT isoenzyme responsible for the glucuronidation of odorants thereby facilitating the termination of receptor occupation and signal transduction by olfactory stimulants (Burchell et al., 1998).

UGT is located in the endoplasmic reticulum of hepatic and extra-hepatic tissue (particularly skin, lung, small intestine and kidney) (Kroemer and Klotz, 1992). These enzymes transfer the glucuronyl group from uridine-5'-diphosphoglucuronate (Figure 1) to many compounds having nucleophilic functional groups of oxygen, nitrogen, sulphur, or carbon. The resulting glucuronide is more water-soluble, less toxic, and more easily excreted than the parent compound. Glucuronides account for most of the detoxified material found in bile and urine. UGTs have evolved to catalyse the glucuronidation of both endogenous compounds (bilirubin, thyroid hormones, sexual hormones and serotonin) and xenobiotics (e.g. acetaminophen and morphine are predominantly cleared in this way). The biological importance of glucuronidation is grossly under-investigated, although, it seems reasonable to postulate that it serves primarily to enhance the elimination of substrates from the body (Clarke and Burchell, 1994). However, the glucuronidates at the D-ring of oestriol, testosterone, and

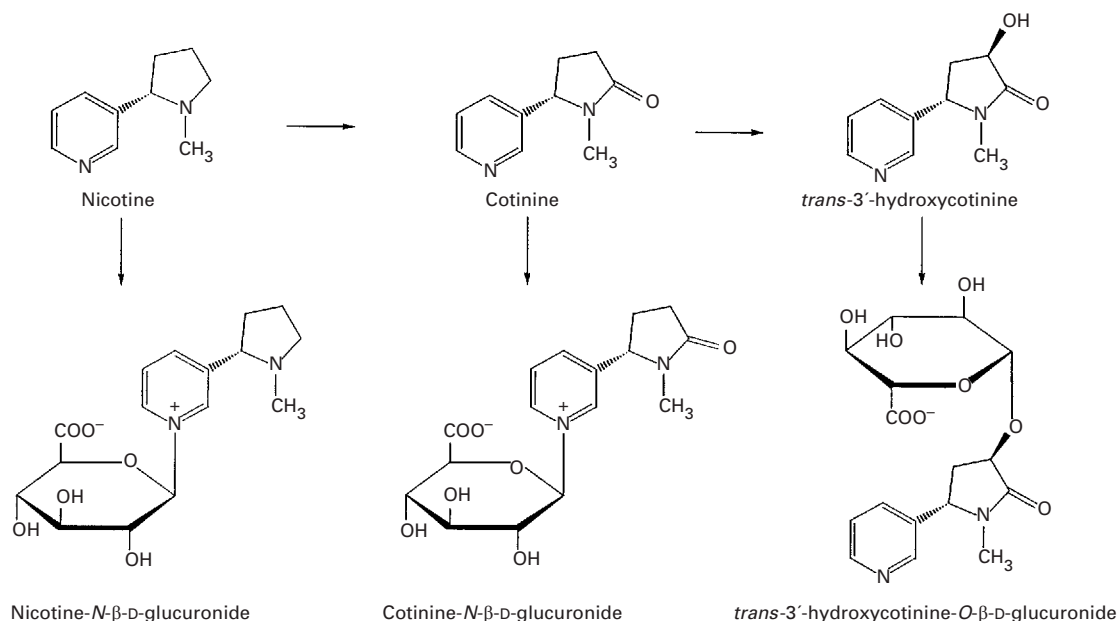


Figure 1. Glucuronidation of nicotine and nicotine metabolites.

dihydroxytestosterone have biological activity and may contribute to cholestasis in animal studies. In contrast, A-ring glucuronidation of these steroids is associated with inactivation. It is also possible that the non-steroidal anti-inflammatory drugs (NSAIDs) and other drugs containing carboxylic acid groups may be converted by glucuronidation to more reactive products that bind to proteins and other cellular macromolecules (Mackenzie et al., 2000). In fact, zomepirac, a NSAID removed from the US market due to high risk of anaphylaxis, undergoes irreversible protein binding after glucuronidation (Liston et al., 2001).

UGTs and their polymorphic variations

At least 24 different human UGT genes have been identified (Burchell et al., 1995; Mackenzie et al., 1997, 2000; Tukey and Strassburg, 2000) and are classified in two subfamilies based on sequence identity, namely the UGT1 subfamily glucuronidates bilirubin and xenobiotic phenols and the UGT2 subfamily glucuronidates steroids and bile acids. Like the CYPs, each species appears to have its own UGTs with different substrates (Walton et al., 2001). Across species, analogous UGTs may have different levels of activity for the same drug.

The UGT1 subfamily is derived from a single gene locus at 2q37 with at least 13 unique varieties of exon 1 and four common exons 2–5 (de Wildt et al., 1999). Each exon 1 is preceded by its own promoter region

and encodes a unique UGT isoform. The messenger RNA encoding each UGT isoform is formed by fusion of one type of exon 1 to the four exons 2–5. The isoenzymes share a conserved domain (3' or C half) and have a variable domain (5' or N half). Gene mutations in the common exon 2–5 region can lead to changes in activity and/or expression of all isoforms, while gene mutations in the unique exon 1 or promoter region may only affect the unique isoform involved (de Wildt et al., 1999). The UGT1A1, UGT1A3, UGT1A4 and UGT1A9 are the best-known isoenzymes and are expressed in the liver. Other isoenzymes of this family appear not to be expressed in the liver but rather in gastrointestinal epitheliums (UGT1A7 in gastric epithelium, UGT1A8 in colonic epithelium, and UGT1A10 in gastric, colonic, and biliary epithelium) (Strassburg et al., 1998). UGT1 liver expression appears to show little inter-individual variation, in contrast to important inter-individual variations in gastric (Strassburg et al., 1998) and small intestinal epithelium (Strassburg et al., 2000). It is probable that UGT1 polymorphisms, particularly those in the promoter area, may have tissue-specific consequences and may be more evident after oral administration. In particular, jejunal UGT activity may have important consequences in drug metabolism variations (Strassburg et al., 2000).

UGT1A1 displays affinity for a variety of compounds besides bilirubin, including steroids and thyroid hormones (Table 1). More than 30 different

Table 1. Possible UGT substrates and inducers

Isoenzyme	Substrates			
	Endogenous	Medications	Probes	Possible inducers
UGT1A1	Bilirubin Catechol oestrogens T4 and rT3	SN-38 Ethenyl oestradiol Buprenorphine Naltrexone	Emodin Bilirubin	Phenobarbital
UGT1A3	Catechol oestrogens	Cyproheptadine Clozapine Amitriptyline		
UGT1A4	Pregnanediol	Many antipsychotics Many TCAs Cyproheptadine Promethazine	Imipramine	Carbamazepine Phenytoin
UGT1A6	Serotonin	Acetaminophen	Acetaminophen 1-Naphthol	Smoking Cruciferous vegetables
UGT1A9	T4 and rT3 Oestrogens	Acetaminophen	Propofol	Smoking Cruciferous vegetables
UGT2B4	Bile acids		Hyodeoxycholic acid	
UGT2B7	Bile acids Androsterone Several androgens ^a Oestrogens Catechol oestrogens Serotonin	Clofibrate Propranolol NSAID Epirubicin Many opioids Zidovudine (AZT)	Morphine	Cruciferous vegetables
UGT2B15	Several androgens ^a			
UGT2B17	Several androgens ^a Androsterone			

^aSeveral androgens: androstenediol, testosterone and dihydrotestosterone.

mutations of the UGT1A1 gene have been associated with the Crigler–Najjar syndrome. Type I is associated with absence of enzyme activity while in type II, UGT1A1 activity is much reduced (de Wildt et al., 1999). In type I (an autosomal recessive disorder), the most typical mutations have been found in exons 2–5, encoding the constant regions of all UGT1 enzymes (Burchell et al., 1998).

According to in-vitro and in-vivo studies, the activity of UGT1A1 in Gilbert's syndrome is reduced to 30% of normal levels (Burchell et al., 2000). Particularly in Caucasians, the polymorphism that leads to Gilbert's syndrome consists of differences in TA repeats in the promoter region (Table 2). The normal wild-type form includes six repeats, (TA)₆TAA. More TA repeats are associated with lower activity. The seven-repeat (TA)₇TAA sequence is found in Caucasian populations while eight repeats (TA)₈TAA is found in African populations. In the latter, a five-repeat

variation associated with increased activity has been described (Iyer, 1999; Iyer et al., 1999; Mackenzie et al., 2000). Thus, in Caucasians, Gilbert's syndrome appears to be strongly associated with homozygosity for allele (TA)₇TAA (designed genotype 7/7). Homozygosity for allele 7 (7/7) is present in 11–13% of Scottish, 17–19% of Canadian Inuits, up to 23% of Africans and less than 3% of Japanese (Burchell et al., 2000). Other mutations may affect UGT1A1 function. Asian populations have a low (TA)₇TAA allele frequency (0.15) but two additional missense mutations in the coding region (Table 2) have been found (Burchell et al., 2000; Iyer, 1999; Lampe et al., 2000; Mackenzie et al., 2000).

The toxicity to an anti-neoplastic drug, irinotecan, may be influenced by the presence of Gilbert's syndrome (Iyer et al., 1999). Specifically, UGT1A1 plays a role in the detoxification of the active metabolite SN-38. In a recent prospective study of 20 patients

Table 2. UGT polymorphic variations

UGT genes	Polymorphisms	Functional effects
UGT1A1	Several in coding region	Crigler–Najjar syndrome (very rare) when patient has mutations in both chromosomes
	(TA) ₇ TAA in promoter	Decreased activity (most Gilbert's syndrome cases in Caucasians have homozygous alleles)
	(TA) ₈ TAA in promoter	Decreased activity (African–Americans)
	(TA) ₅ TAA in promoter	Increased activity (African–Americans)
	G71R ^a in coding region	Decreased activity (Asians)
UGT1A6	Y486D ^b in coding region	Decreased activity (Asians)
	T181A ^c in coding region	Both mutations combined cause lower activity in vitro; probably no clinical significance
UGT2B4	R184S ^d in coding region	
	D485E ^e in coding region	It is not clear that is associated with changes in functional activity
UGT2B7	F109L + F396L ^f in coding region	Rare. Lower activity in vitro but probably with no clinical significance
	Y268H ^g in coding region	Probably no functional effects in spite of earlier suggestion of being functional
UGT2B15	D85Y ^h in coding region	No functional effects

^a Change from glycine (G) to arginine (R) at position 71; ^b change from tyrosine (Y) to aspartate (D) at position 486; ^c change from threonine (T) to alanine (A) at position 181; ^d change from arginine (R) to serine (S) at position 184; ^e change from aspartate (D) to glutamate (E) at position 485; ^f change from phenylalanine (F) to leucine (L) at positions 109 and 396; ^g change from histidine (H) to tyrosine (Y) at position 268; ^h change from aspartate (D) to tyrosine (Y) at position 85.

with solid tumours, Iyer et al. (2002) found that patients with the (TA)₇TAA polymorphism had significantly lower SN-38 glucuronidation rates and more adverse drug reactions. Patients homozygous for allele (TA)₇TAA (genotype 7/7) and heterozygous with one allele (TA)₇TAA, and one allele (TA)₆TAA (genotype 6/7) have respectively 50 and 25% decreases in glucuronidation of SN-38 when compared to patients homozygous for allele (TA)₆TAA (genotype 6/6) (Iyer, 1999). Two other recent pharmacokinetic studies with patients taking irinotecan also supported the view that this polymorphic variation influences SN-38 glucuronidation (Ando et al., 2002; Xie et al., 2002).

Myaoka et al. (2000a,b) have suggested that schizophrenia is associated with Gilbert's syndrome in Japan, unfortunately, they did not verify the presence of Gilbert's syndrome with genetic testing and only used the hyperbilirubinaemia to make the diagnosis. It is not possible to rule out that other environmental factors including medications or medications remaining in the body after their discontinuation may explain the differences in hyperbilirubinaemia between schizophrenic patients and other patients.

UGT1A3 (Table 1) catalyses glucuronidation of primary, secondary, and tertiary amines, coumarins, flavinoids, and oestrones (Green et al., 1998; Liston

et al., 2001). It shares more than 90% of its amino-acid sequence with UGT1A4, but it has low efficiency compared to UGT1A4 (Green et al., 1998; Liston et al., 2001).

UGT1A4 (Table 1) catalyses N-glucuronidation of tertiary amines and other xenobiotics (Burchell and Coughtrie, 1997). The UGT1A4 isoform may be the most important isozyme for the glucuronidation of some tricyclic antidepressants (TCAs) and some typical and atypical antipsychotics (Green et al., 1998; Green and Tephly, 1998). Imipramine may be a probe for UGT1A4 (Burchell and Coughtrie, 1997).

UGT1A6 (Table 1) metabolizes planar phenolic compounds (Burchell et al., 2000). Two missense mutations have been identified (Table 2). The presence of both mutations in a single allele was detected in up to 30% of the population with some ethnic variations (Lampe et al., 2000). In-vitro studies using cultured cells with both mutations suggest that they may affect function but it is unclear whether this decrease in function has any in-vivo implications (Mackenzie et al., 2000).

UGT1A9 is more promiscuous than UGT1A6 as it metabolizes many bulky phenols. The substrates include drugs such as acetaminophen, and some endogenous compounds (Table 1).

The UGT2 family has subfamilies. The olfactory-specific isoforms are included in the UGT2A subfamily. In humans, UGT2A1 is expressed in olfactory epithelium, brain, and fetal lung (Tukey and Strassburg, 2000). The UGT2B subfamily includes metabolic enzymes that are responsible for the glucuronidation of steroids and bile acids. The UGT2Bs are synthesized from a series of at least five similar genes located in a cassette on the chromosome 4q13 (Burchell et al., 2000). The UGT2B4 gene has been isolated and has five introns and six exons (17.5 kb). The UGT2B7 is also located on chromosome 4. UGT2B15 and UGT2B17 metabolize androgens and are also mapped there.

UGT2B4 metabolizes steroids and bile acids (Table 1). Two polymorphisms with ethnic variations have been identified (Table 2) but it is unclear whether they affect function (Lampe et al., 2000; Mackenzie et al., 2000).

UGT2B7 (Table 1) metabolizes steroids, bile acids and many opioids (Burchell et al., 1995; Burchell and Coughtrie, 1997; Liston et al., 2001). A polymorphic variation, H268Y (Table 2), has been described with different frequencies in Caucasians and Japanese subjects (Lampe et al., 2000). Patel et al. (1995a) showed that ketoprofen, as well as other substrates of UGT2B7, competitively inhibit the (*S*)-oxazepam glucuronidation. Following that, Patel et al. (1995b) suggested that 10% of Caucasians are poor glucuronidators of *S*-oxazepam. They proposed that the UGT2B7-H268Y polymorphism may account for this difference in *S*-oxazepam metabolism. In an in-vitro study, Coffman et al. (1998) found that oxazepam is a poor substrate for UGT2B7. Several recent studies suggest that H268Y polymorphic variation does not influence metabolism of UGT2B7 substrates, including morphine (Bhasker et al., 2000; Coffman et al., 1998; Holthe et al., 2002; Innocenti et al., 2001).

UGT2B15 metabolizes a wide range of phenols including steroids, and food-derived flavones and flavonoids. Two polymorphic variations (Table 2) with ethnic variations have been described. Each allele accounts for approximately half of the alleles in Caucasians. As both alleles have similar substrate specificities and kinetic characteristics, it is extremely unlikely that this polymorphism has clinical significance (Mackenzie et al., 2000).

Other factors may influence UGT function besides polymorphic gene variations

Hepatic glucuronidation undergoes significant changes during fetal and neonatal development. Therefore, age-adapted drug therapy may be required. UGTs

do not appear to be detected in fetal liver until 20 wk gestation. After 6 months of life UGTs are present, but UGT1A9 and UGT2B7 appear to show remarkable lower expression even beyond 2 years (Leakey et al., 1987; Strassburg et al., 2002).

Several drugs metabolized by glucuronidation appear to inhibit UGTs in a non-specific way. Lorazepam, oxazepam, TCAs, valproic acid, ketoprofen, and probenecid appear to inhibit several UGTs. No specific UGT inhibitors have been identified but are now being investigated (Golovinsky et al., 1998).

In-vitro studies (Bock et al., 1999; Munzel et al., 1999) suggest that the polycyclic aromatic hydrocarbons found in tobacco smoke appear to cause enzymic induction at UGT1A6 and UGT1A9 by binding to an intracellular aryl hydrocarbon receptor (Fuhr, 2000). According to these studies, some food antioxidants, such as those found in cruciferous vegetables (e.g. broccoli) appear to induce UGT1A6, UGT1A9 and UGT2B7 (Munzel et al., 1999). Phenobarbital is an inducer of UGT1A1 (Bock et al., 1999) and has been used to treat neonatal hyperbilirubinaemia. Carbamazepine and phenytoin appear to be UGT1A4 inducers, since they are inducers of lamotrigine, a UGT1A4 drug not metabolized by CYP1A2.

According to studies in rats, some hormones, e.g. thyroid hormones and growth hormone, may influence the activity of UGTs. In humans, it has been shown that hypothyroidism may decrease the glucuronidation of oxazepam (Sonne, 1993). Little attention has been paid to the effects of sexual hormones on UGTs (Gueraud and Paris, 1998). It is believed that androgens may influence its own metabolism by influencing UGT activity in different tissues (Belanger et al., 1998).

Lack of UGT specificity

Current knowledge holds that each UGT has the capacity to glucuronidate a large range of substrates (Table 1) and that one compound may be glucuronidated by several UGTs; however, some substrates are solely or predominantly glucuronidated by a single UGT (e.g. bilirubin and UGT1A1) (Mackenzie et al., 2000).

The lack of specificity of UGT is well exemplified by acetaminophen glucuronidation. UGT1A9 may be the predominant UGT to glucuronidate this compound in typical doses, while UGT1A6 may be more active at low concentrations. UGT1A1 may also intervene with toxic concentrations (Court et al., 2001).

In the liver, the active T4 and the inactive rT3 appear to be substrates of UGT1A1, while in extrahepatic

tissues UGT1A9 may also intervene (Findlay et al., 2000). Hyodeoxycholic acid is a substrate for UGT2B4 but it can be glucuronidated by other UGTs, particularly UGT2B7.

There is substantial overlap between different UGTs regarding the metabolism of sexual steroids. An *in-vitro* study (Turgeon et al., 2001) demonstrated that androstenediol, testosterone, and dihydrotestosterone were glucuronidated by UGT2B7, UGT2B15 and UGT2B17. Androsterone, the main androgen metabolite, was glucuronidated by UGT2B7 and UGT2B17. Oestrogens, including oestradiol, appear to be conjugated by UGT2B7 and UGT1A9 (Albert et al., 1999; Turgeon et al., 2001). Catechol oestrogens (the most potent naturally occurring inhibitors of catecholamine metabolism) appear to be conjugated by UGT1A1, UGT1A3 and UGT2B7 (Cheng et al., 1998; Turgeon et al., 2001).

Psychopharmacological medications metabolized by UGT enzymes

The pharmacokinetic and pharmacodynamic aspects of the action of glucuronides of psychopharmacological compounds has not been well studied in humans (Hawe, 1998). The literature provides limited information in this area (Table 3). It is generally thought that glucuronidation is a way of detoxification of a compound but this may not always be true. Sometimes glucuronides are not rapidly excreted and accumulation during long-term therapy occurs with a variety of compounds. Some researchers have speculated that glucuronides may represent an internal storage system from which the active parent compound may be recruited by deconjugation (Kroemer and Klotz, 1992). There have been some reports of pharmacological activity and toxicity of certain glucuronides (Clarke and Burchell, 1994; Kroemer and Klotz, 1992). In an isolated study the administration of a glucuronide, of the psychiatric medication amitriptyline, demonstrated its activity by inducing the rapid onset of side-effects (Breyer-Pfaff et al., 1990).

UGT metabolizes some of the typical antipsychotics, such as the phenothiazines, loxapine and haloperidol (Shen, 1997). An earlier study suggested a link between the glucuronidation activity with side-effects of phenothiazines (Wright et al., 1983). According to Green and Tephly (1998) chlorpromazine, trifluoperazine, and loxapine are substrates of UGT1A4. The possibility that glucuronidation may be an important metabolic pathway for haloperidol has recently been receiving attention. In a review, Kudo and Ishizaki (1999) described that glucuronidation

of haloperidol accounts for 50–60% of human metabolism. Haloperidol metabolism is induced by smoking (Perry et al., 1993; Shimoda et al., 1999). Haloperidol does not appear to be metabolized by CYP1A2 (an enzyme induced by smoking) (Mihara et al., 2000). Pan and Belpaire (1999) suggested that smoking may induce haloperidol metabolism by inducing UGTs.

Glucuronidation may also be an important pathway for clozapine (Luo et al., 1994). According to Green and Tephly (1998), clozapine and desmethylclozapine (the main clozapine metabolite) are substrates of UGT1A4. Clozapine is also a substrate of UGT1A3. In a more recent *in-vitro* study, Breyer-Pfaff and Wachsmuth (2001) described that clozapine-5-*N*-glucuronide and desmethylclozapine-5-*N*-glucuronide are found in small percentages in the urine (<1% of clozapine doses). However, these low concentrations may reflect that as 5-*N*-glucuronide clozapine metabolites are labile under acidic conditions, they can, therefore, be deconjugated in the urine.

Olanzapine-10-*N*-glucuronide appears to make up approx. 25% of the metabolic clearance of olanzapine (Callaghan et al., 1999; Hagg et al., 2001; Kassahun et al., 1998). Markowitz et al. (2002) suggested in a recent clinical study using probenecid, a UGT inhibitor, that olanzapine (but not risperidone) is a substrate of UGT, possibly UGT1A4. An *in-vitro* study also supported the role of UGT1A4 (Linnet and Olesen, 2001). Carbamazepine induces olanzapine metabolism leading to considerable decrease (30–50%) of plasma olanzapine concentration (Licht et al., 2000; Lucas et al., 1998; Olesen and Linnet, 1999). The inductive effects of carbamazepine had been posited to be mediated by CYP1A2 induction (Callaghan et al., 1999; Lucas et al., 1998). More recently, Linnet and Olsen (2002) have demonstrated that the induction of glucuronidation may be more important than the CYP1A2 induction. They measured plasma olanzapine and olanzapine-10-*N*-glucuronide concentrations and found that, in patients co-medicated with carbamazepine, plasma olanzapine-10-*N*-glucuronide accounted on average for 79% of plasma concentrations. In patients taking olanzapine only, olanzapine-10-*N*-glucuronide concentrations accounted on average for only 43% of plasma concentrations. They also suggested that the other glucuronide, olanzapine-4-*N*-glucuronide, is found in very low concentrations in plasma.

The potent inhibition of glucuronidation of sexual steroids by tertiary amine drugs such as chlorpromazine, amitriptyline and imipramine may be an important issue (Sharp et al., 1992). Direct inhibition of UGTs

Table 3. Glucuronidation of psychiatric drugs and of substances liable to be abused

Substrates	Glucuronides	UGT	Metabolism (%)
Antidepressants			
Amitriptyline	Amitriptyline- <i>N</i> -glucuronide	UGT1A4/A3	25% ^a
Chlorimipramine	8-OH-chlorimipramine-glucuronide	UGT1A4	–
	8-OH-norchlorimipramine-glucuronide	–	–
Doxepin	–	UGT1A4	> 20% ^b
Imipramine	–	UGT1A4	–
Nortriptyline	E-10-hydroxynortriptyline-glucuronide	–	–
Trazadone	–	–	< 1% ^c
Antipsychotics			
Chlorpromazine	Chlorpromazine- <i>N</i> -glucuronide	UGT1A4	–
Clozapine	Clozapine-5- <i>N</i> -glucuronide	UGT1A4/A3	1% ^d , 3% ^c for
	Norclozapine-5- <i>N</i> -glucuronide	UGT1A4	both metabolites*
Haloperidol	Haloperidol-glucuronide	–	50–60% ^e for
	Reduced haloperidol-glucuronide	–	both metabolites
Loxapine	–	UGT1A4	2% ^c
Olanzapine	Olanzapine-10- <i>N</i> -glucuronide	UGT1A4	> 25% ^f
	Olanzapine-4- <i>N</i> -glucuronide	–	> 5% ^f
Trifluoperazine	–	UGT1A4	–
Benzodiazepines			
Lorazepam	Lorazepam-hydroxy-glucuronide	UGT2B7?	> 80% ^g , 92% ^a
Oxazepam	Oxazepam-hydroxy-glucuronide	UGT2B7?	86% ^a
Mood stabilizers			
Carbamazepine	Carbamazepine-10,11- <i>trans</i> -diol-glucuronide	–	15% ^h
Lamotrigine	Lamotrigine 2- <i>N</i> -glucuronide	UGT1A4	65% ^h , 86% ⁱ , 89% ^a ,
	Lamotrigine 5- <i>N</i> -glucuronide	–	for both metabolites
Valproic acid	Valproate-glucuronide	Several?	33% ^a , 40% ^h , ≤ 60% ⁱ
	Several metabolite-glucuronides	–	–
Substances liable to be abused and related medications			
Buprenorphine	–	UGT2B7/1A1	–
Codeine	Codeine-6- <i>O</i> -glucuronide	UGT2B7	45% ^a , 70% ⁱ
Morphine	Morphine-6-glucuronide	UGT2B7	55% ^a for
	Morphine-3-glucuronide	UGT2B7	both metabolites
Naloxone	–	UGT2B7	60% ^a , 60–70% ⁱ
Naltrexone	–	UGT2B7/1A1	–
Nicotine	Nicotine-glucuronide	–	4% ^j
	Cotinine-glucuronide	–	13% ^j
	3'-hydroxycotinine-glucuronide	–	7% ^j

* Low percentage may reflect deglucuronidation in urine. –, Indicates that information is not described in the literature.

?, Indicates uncertainty. ^a Miners and Mackenzie (1991); ^b Hawes (1998); ^c Luo et al. (1995); ^d Breyer-Pfaff and Wachsmuth (2001); ^e Kudo and Ishizaki (1999); ^f Kassahun et al. (1998); ^g Samara et al. (1997); ^h Anderson (1998); ⁱ Bertz and Granneman (1997); ^j Benowitz and Jacob (1997).

could significantly alter the production of steroid glucuronides and may contribute to the sexual side-effects of antipsychotics or TCAs (Sharp et al., 1992).

Imipramine, amitriptyline, chlorimipramine and doxepin are substrates of UGT1A4 (Green et al., 1998; Green and Tephly, 1998). A recent in-vitro imipramine study using 14 human liver microsomes found inter-individual glucuronidation activity differences at most

of 2.5-fold (Nakajima et al., 2002). A study of plasma levels in 108 Japanese patients taking chlorimipramine showed that there were 28-fold variations in glucuronidation and that benzodiazepine intake and female gender appear to be associated with decrease in glucuronidation (Shimoda et al., 1995). The *N*-dimethylated metabolites, desimipramine, and nortriptyline, are not substrates of UGT1A3 or UGT1A4 (Green et al.,

1998; Green and Tephly, 1998) but some of the nortriptyline metabolites appear to be eliminated by glucuronidation (Liston et al., 2001). Trazadone also appears to be metabolized by glucuronidation (Luo et al., 1995). Two case reports have suggested that some selective serotonin reuptake inhibitors may inhibit UGTs (Haffen et al., 1999; Kauffman and Gerner, 1998).

Most benzodiazepines are metabolized by CYPs and then by UGTs. However, lorazepam and oxazepam are only metabolized by glucuronidation. As described previously, Patel et al. (1995b) suggested that 10% of Caucasians are poor glucuronidators of 5-oxazepam but it is not clear whether UGT2B7 metabolizes oxazepam. Lorazepam is not a substrate of UGT1A1, but appears to be a non-competitive inhibitor that may have a negative influence in patients with Gilbert's syndrome who already have an impaired glucuronidation of bilirubin (Burchell et al., 2000). In another study, the co-administration of valproic acid was associated with mild and not clinically significant increases of lorazepam levels (Samara et al., 1997). A recent case report of a coma after a combination of lorazepam and valproic acid questions the possibility that in some patients this combination may have clinical significance (Lee et al., 2002).

There is an even greater relationship between anti-epileptics/mood stabilizers and glucuronidation. Phenytoin, primidone and phenobarbital can induce glucuronidation (Hachad et al., 2002). Glucuronidation is probably the most important metabolic pathway for valproic acid accounting for 33–60% of its metabolism (Table 3). It has been suggested that valproic acid may be a substrate for UGT2B7 (de Wildt et al., 1999; Liston et al., 2001), UGT1A3 (Liston et al., 2001) or UGT1A6 and UGT1A9 (Burchell et al., 2000).

The UGTs account for approx. 15% of carbamazepine metabolism (Anderson, 1998). Oxcarbazepine is also metabolized by glucuronidation (Baruzzi et al., 1994). Valproic acid inhibits carbamazepine metabolism. Bernus et al. (1997) found, in 17 patients, that this inhibition is partly explained by an inhibition of the glucuronidation of a carbamazepine metabolite. Carbamazepine, an inducer of some metabolic enzymes including glucuronidation enzymes, increases the glucuronidation of valproic acid.

Lamotrigine is a weak inducer of glucuronidation and of its own metabolism. Glucuronidation is the major metabolic pathway, accounting for up to 65–90% of lamotrigine metabolism (Table 3). The main urine metabolite is the inactive 2-*N*-glucuronide (Hachad et al., 2002). Recent reviews (Burchell et al., 2000; Liston et al., 2001) suggest that UGT1A4 may

metabolize lamotrigine. Co-administration with valproic acid decreases lamotrigine metabolism and may increase the risk of a skin rash associated with lamotrigine. In clinical settings, it is important to decrease the initial dose of lamotrigine in patients taking valproic acid (Page et al., 1998). It has also been suggested that sertraline increased lamotrigine levels and toxicity by inhibiting glucuronidation (Kauffman and Gerner, 1998). UGT inducers such as phenytoin, carbamazepine, and phenobarbital increase lamotrigine metabolism. Hachad et al. (2002) suggested that the inhibitory effect of valproic acid in lamotrigine metabolism is stronger than inductive effects of carbamazepine and phenobarbital. However, when valproic acid is combined with phenytoin, the effects of both drugs on lamotrigine metabolism compensate for each other.

UGTs and substance abuse

Recently it has been found that a lack of certain metabolic enzymes may influence substance addiction. CYP2D6 activates codeine and transforms it into morphine; poor CYP2D6 metabolizers, lacking CYP2D6, may be protected from codeine abuse (Tyndale et al., 1997). Similar associations with CYP2A6 have been reported for nicotine. Nicotine is primarily metabolized to its main metabolite, cotinine, by CYP2A6. Cotinine is further metabolized by CYP2A6 to *trans*-3'-hydroxycotinine. It appears that East Asians who are deficient in CYP2A6 smoke less cigarettes (Raunio et al., 2001; Tyndale and Sellers, 2002).

Glucuronidation may also influence opioid and nicotine addiction. Racial differences in glucuronidation may influence codeine use (Kroemer and Klotz, 1992). Morphine is glucuronidated in a stereoselective manner to morphine-3-glucuronide and morphine-6-glucuronide. The administration of morphine-6-glucuronide by the intrathecal or intracerebroventricular routes reveals that this compound is 45–800 times more potent than the parent drug (Christup, 1997). Given systemically, it appears to be twice as potent as morphine in animal models and human beings. Morphine-3-glucuronide appears to be an antagonist of morphine and has been suggested to contribute to side-effects such as the hyperalgesia and myoclonus during high-dose morphine treatment in rats (Christup, 1997). It is surprising that morphine glucuronides have any CNS activity at all. As a rule, glucuronides are considered highly polar compounds unable to cross the blood–brain barrier. However, it is clear that morphine glucuronides, in spite of the high polarity, do cross the blood–brain barrier, but the mechanism

and extent are unclear. It has been suggested that morphine glucuronides may mediate morphine intoxication in some pathological conditions such as renal failure. In renal failure, the glucuronides will not be eliminated in urine, so they are available for deconjugation (Kroemer and Klotz, 1992).

Morphine, codeine, naloxone, naltrexone, and buprenorphine appear to be substrates of UGT2B7 (de Wildt et al., 1999; Liston et al., 2001). Naltrexone and buprenorphine also appear to be UGT1A1 substrates (King et al., 1996). During an in-vitro study, Whalstrom et al. (1994) found that concentrations of TCAs, close to those achieved in patients' plasma, inhibited morphine glucuronidation. This may potentiate analgesia but can also produce adverse side-effects.

Up to 25% of nicotine metabolism can be explained by glucuronidation (Benowitz and Jacob, 1997). Nicotine suffers glucuronidation (Byerly et al., 2000) and the same happens for the main metabolites cotinine and 3'-hydroxycotinine (Figure 1). Racial differences in nicotine clearance may be affected by UGT activity. African-Americans do not eliminate nicotine as well as Caucasians (Perez-Stable et al., 1997; Caraballo et al., 1998). Benowitz et al. (1999) measured urine concentration of nicotine metabolites including the glucuronides of nicotine, cotinine, and 3'-hydroxycotinine. They described slow metabolizers for nicotine and cotinine glucuronidation as overrepresented among African-Americans in their sample. They also indicated that the same enzyme probably performed the N-1-glucuronidation of nicotine and cotinine, but the O-glucuronidation of 3'-hydroxycotinine is probably conducted by another UGT.

The problem with measuring nicotine metabolite-glucuronides is that nicotine-glucuronide (Byrd et al., 2000) and cotinine-glucuronide have been synthesized (Caldwell et al., 1992) and can be used as analytical standard. However, 3'-hydroxycotinine-glucuronide has not been synthesized and cannot be used as standard in analytical methods (Ghosheh et al., 2000). The first study measuring plasma cotinine glucuronide and 3'-hydroxycotinine-glucuronide (de Leon et al., 2002) suggested, as did the urine study by Benowitz et al. (1999), that the glucuronidation of cotinine and 3'-hydroxycotinine is conducted by two different UGTs. Moreover, the low stability of plasma cotinine glucuronide suggests it may undergo in-vivo deconjugation by β -glucuronidase (de Leon et al., 2002). A second study of plasma nicotine metabolites compared American Caucasians and African-American smokers (de Leon et al., In Press). Although it was too small, it was compatible with the findings of Benowitz et al. (1999) that African-Americans may be

overrepresented among the slow metabolizers for the glucuronidation of cotinine.

Benowitz and Jacob (2000) found that cigarette smoking markedly induced O-glucuronidation of 3'-hydroxycotinine but did not influence N-1-glucuronidation of nicotine and cotinine. Recently, in an in-vitro study, Ghosheh and Hawes (2002) found that cotinine or nicotine were not substrates of ten UGTs tested.

UGTs in the brain

The UGT1A family probably conjugates serotonin since some patients with Crigler-Najjar syndrome are poor glucuronidators of this compound (Burchell and Coughtrie, 1997). King et al. (1999) suggested that serotonin may be a substrate of brain UGT1A6 (and of UGT2B7 that is less efficient).

The presence of large quantities of dopamine glucuronide in rat CSF suggests the involvement of UGTs in the metabolism of dopamine of central origin (Wang et al., 1983). However, it would be important to know how active this pathway is in humans (Wang et al., 1983).

Animal studies have identified small concentrations of UGTs in brain tissue. However, UGTs and other metabolic enzymes appear to be in higher concentrations at brain capillaries and they appear to be associated with the blood-brain barrier (Minn et al., 1991). A few human brain studies have shown a limited concentration of UGTs in brain tissue. However, these human studies have a major limitation in that they tend to use UGT substrates extrapolated from animal models to identify UGTs in brain tissue. The identification of human UGT genes will help determine whether or not they are expressed in the human brain, and their location.

Very small concentrations of metabolic enzymes, CYPs or UGTs, may have a major effect if they are located to protect a specific set of neurons from a toxin. The small concentration in some brain areas may be not important in the global metabolism when compared to the liver metabolic enzymes. However, if a dietary compound has specific neurotoxicity by interfering with a specific neurotransmitter receptor, the metabolic enzyme located in that area of the brain may be important in order to detoxify any remaining toxin escaping detoxification by the liver or other organs (Britto and Wedlund, 1992).

In summary, this review tries to illustrate the importance of glucuronidation and the implications for psychiatry. Hopefully, when a psychiatrist or a psychiatric researcher sees the word 'glucuronidation' or

'UGT' in an article or other publication, they will not dismiss the subject lightly. In the next 10 years, advances in genetic mapping are going to provide new, revolutionary, and shocking findings in our understanding of the genetics of severe mental illnesses and glucuronidation genes may prove important to understanding or treating these conditions. For the sceptics who feel that glucuronidation genes may have little significance in the field of psychiatry, imagine what he/she would have thought several years ago if someone tried to convince him/her that a protein related to cholesterol metabolism (ApoE) was related to Alzheimer's disease. In the future, the impact of UGT genetic variability should be evaluated in concert with polymorphic variations of CYP and other phase I enzymes.

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