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Review Article

**CYTOCHROME P450 – ROLE IN DRUG METABOLISM AND
GENETIC POLYMORPHISM**

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Abstract:

The cytochrome P450 isoenzymes are a super family of haemoproteins that are terminal oxidases of mixed function oxidase system embedded primarily in the lipid bilayer of the endoplasmic reticulum (ER) of hepatocytes. They are so named because they are bound to membrane within a cell (cyto) and contain a haeme pigment (chrome P) that absorb light at a wavelength 450 nm when exposed to carbon monoxide. They are essential for metabolism of large number of endogenous and exogenous compounds. It has been estimated that 90% of human drug oxidation can be attributed to six main enzymes CYP 1A2, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 and CYP 3A4/5 with the two most significant enzymes being CYP 3A4 and CYP 2D6. Recently, the cytochrome isoenzymes have been shown to be important in the synthesis of steroid hormones, bile acids, arachidonic acid and in CNS function. Cytochrome P450 enzymes can be inhibited or induced by drugs, resulting in clinically significant drug-drug interactions that can cause anticipated adverse drug reactions or therapeutic failure. Genetic variability (polymorphism) in the enzymes may influence a patient's response to commonly prescribed drugs. Genotype tests for cytochrome P450 polymorphism have primarily been used for research purpose or clinical drug trials.

Keywords: cytochrome P450, endoplasmic reticulum, metabolism, isoenzymes, polymorphism.

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INTRODUCTION:

The CYTOCHROME P450 isoenzymes are a super family of haemoproteins that are the terminal oxidases of the mixed function oxidase system embedded primarily in the lipid bilayer of the endoplasmic reticulum of hepatocytes. These isoenzymes are so called because they have a spectrophotometric absorption peak at or near 450 nm when bound and reduced by carbon monoxide [1].

It is entrenched that the cytochrome enzymes in humans are engaged with the metabolism of exogenous substances (drugs, alcohols, antioxidants, natural solvents, analgesics, colors, environmental toxins and chemicals) produce metabolites which might be poisonous or carcinogenic [2]. They are additionally imperative in the oxidative, peroxidative and reductive metabolism of endogenous physiological compounds for example, steroids, bile acids, unsaturated fats, prostaglandins, biogenic amines and retinoids. Figure 1 shows the cytochrome P450 Monooxygenase system.

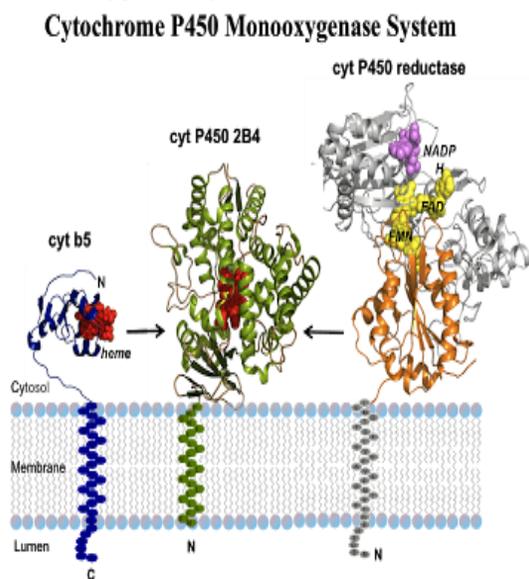


Fig 1: Cytochrome P450 Monooxygenase System

Family Sub Individual
 Family Gene

CYP2D6

Fig 2: nomenclature of cytochrome P450 enzyme

NOMENCLATURE

A general nomenclature is given based on amino acid sequence by Nebert and partners. This framework is generally acknowledged and it group the isoenzymes

and genes into families and subfamilies with the prefix 'CYP' to assign cytochrome P450 isoenzymes in all species (aside from *Drosophila* and mouse quality where 'Cyp' is used) [3]. The current system of nomenclature for the different CYP isozymes utilizes a three-layered classification depending on the conventions of molecular biology. In this framework, cytochrome P450 proteins from all sources having over 40% identity in amino acids are set in a similar family and this is assigned by an Arabic numeral.

A subfamily comprises of enzymes in which the amino acid sequence is over 55% indistinguishable and this is assigned by a capital letter. Finally, an Arabic numeral after the letter signifies the individual enzyme and the gene related with the enzyme is meant in italics. For instance, the CYP 2 family has a various subfamilies, for example, CYP 2C, CYP 2D and CYP 2E. Each enzyme is indicated by a numeral, as in CYP 2D6, and the gene is known as CYP 2D6. The benefit of this classification is that basically indistinguishable or profoundly comparative cytochrome P450s are effortlessly distinguished from their sources or their synergist actions. Figure 2 shows the nomenclature of CYP 450 enzyme.

CLASSIFICATION

A list of 481 P450 genes and 22 pseudo genes has been accounted for. Of the 74 quality families depicted, 14 families have been accounted for in humans and 20 subfamilies have been mapped in the human genome [4]. It has been assessed that 90% of human drug oxidation can be ascribed to six primary compounds (CYP 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4/5). The activities of the CYP 2C19 and CYP 2D6 compounds are biomedically circulated in the population, permitting characterization of people as either extensive metabolizers (EM) or poor metabolizers (PM) [5-6]. The most significant CYP isoenzymes are CYP 3A4 and CYP 2D6.

CYP 1 Family**CYP 1A1 AND CYP 1A2**

The CYP 1A family comprises of two proteins, 1A1 and 1A2. CYP 1A1 isn't fundamentally present in the liver. It is discovered for the most part in the lungs, mammary organs, placenta and lymphocytes. It is a enzyme engaged with the inactivation of procarcinogens and is exceedingly initiated by polycyclic aromatic hydrocarbons (PAHs), which are found in cigarette smoke [7]. There is a strong relationship between the action of CYP 1A1 and the danger of lung cancer. CYP 1A2 is expressed mostly in the liver and is prompted by cigarette smoking [8]. It is additionally actuated by the ingestion of a few foodstuffs, for example, cruciferous vegetables and grilled or charbroiled substance [09]. Some

medications, for example, omeprazole may instigate CYP 1A2 activity [10]. Drugs which are known to be metabolized by CYP 1A2 include theophylline, caffeine, imipramine, paracetamol and phenacitin [11]. Alteration in CYP 1A2 action, for instance by smoking, may change the prerequisites for theophylline among asthmatics and haloperidol caffeine metabolism is induced by smoking and explains the increased tolerance to caffeine among smokers [12].

CYP 2 Family

CYP 2A6, CYP 2C9, CYP 2C19, CYP 2D6 and CYP 2F

CYP 2A6: CYP 2A6 is known as coumarin hydroxylase, is a generally insignificant enzyme, one of the substrates metabolized by this enzyme is nicotine [13].

CYP 2C: CYP 2C subfamily is amongst the most imperative families and comprises basically of two compounds, CYP 2C9 and CYP 2C19.

CYP 2C9: Among the substrates of CYP 2C9 is the anticoagulant warfarin, which exists in two isoforms of which the S-shape is the most essential and this is metabolized by CYP 2C9 [14]. Other drugs metabolized by CYP 2C9 are nonsteroidal anti-inflammatory drugs (including COX-2 specific inhibitors); the hypoglycemic tolbutamide, phenytoin and the angiotensin-II receptor antagonist losartan.

CYP 2C19: It utilizes various substrates including the benzodiazepine diazepam, proton pump inhibitor omeprazole, propranolol and the energizer amitriptyline [15]. It has been shown that poor metabolizers who are recommended proton-pump inhibitor omeprazole as a component of treatment against *Helicobacter pylori* disease may have altogether better clinical results when contrasted with a gathering of patients homozygous for the ordinary, i.e. wild-type, alleles [16].

CYP 2D6: Drugs metabolized by this enzyme including anti arrhythmic, for example, flecanide and encainide, tricyclic antidepressants, some beta-blockers and various particular serotonin reuptake inhibitors. It is of specific importance to sedatives in light of the fact that various usually utilized analgesics, including codeine and tramadol, are metabolized by this enzyme [17]. Previously named debrisoquine hydroxylase, was one of the first to be classified after acknowledgment that the metabolism of the hypotensive agent debrisoquine was anomalous in an extent of humans [18]. It was renamed CYP 2D6 after the parent gene was cloned and the enzyme sorted [19]. To date, more than 70 polymorphisms of CYP 2D6 have been indexed. The dominant parts of these enzymes result in a poor metabolizer phenotype instead of the normal, i.e. extensive metabolize phenotype. Also, various

genotypes exist where gene duplication brings about an ultra quick process status. These patients eliminate CYP 2D6 substrates quicker than normal and if there should be an occurrence of pro drugs, for example, codeine are at more serious danger of sedative related effects [20].

CYP 2E1: The CYP 2E family contains just a single enzyme, CYP 2E1 (dimethyl nitrosamine N-demethylase), which is responsible for metabolism of some natural compounds, for example, liquor and carbon tetrachloride and in addition the halogenated sedative specialists halothane, enflurane, diethyl ether, trichloroethylene, chloroform, isoflurane and methoxyflurane [21]. It is additionally responsible for the breakdown of numerous low atomic weight poisons and cancer-causing agents, a large number of which are utilized as a part of manufacturing and cleaning industry, including benzene, styrene, vinyl chloride and N-nitrosamines. Some of these substances are expert cancer-causing agents which are activated by CYP 2E1. Because of the key part of CYP 2E1 in the biodegradation of various ecological cancer-causing agents, the enzyme has been examined nearly in connection to the causation of neoplasia. There is additionally mounting proof that CYP 2E1 might be a key factor in the pathogenesis of alcoholic liver disease [22].

CYP 3 Family

CYP 3A4: CYP 3A4 is the most inexhaustible drug metabolizing enzyme in humans responsible for the breakdown of more than 120 various medications and in this manner it is a vital area for examine regarding enzyme based medication interactions. Among the drugs metabolized are narcotics, for example, midazolam, triazolam and diazepam, amitriptyline and imipramine, the antiarrhythmics amiodarone, quinidine, propafenone and disopyramide, the antihistamines terfenadine, astemizole and loratidine, calcium channel antagonists, for example, diltiazem and nifedipine and different antimicrobials and protease inhibitors [23].

DISTRIBUTION OF CYP450 ENZYMES

It is notable that the cytochrome P450 framework is related with hepatic metabolism. CYP 1, 2 and 3 families represent 70% of the total hepatic P450 content and are responsible of most medication metabolism. Based on their demeanor in the liver, it gives the idea that CYP 3A represents around 30% of the total hepatic P450; CYP 2 around 20%; CYP 1A2 around 13%; CYP 2E1 around 7%; CYP 2A6 around 4%; and CYP 2D6 around 2%. Extra hepatic cytochrome P450 has been recognized in an extensive variety of tissues such as small intestine, pancreas, brain, lung, adrenal gland, kidney, bone marrow, pole cells, skin, ovary and testis. The

cytochrome P450 isoenzymes are available all through the mucosa of the gut [24, 25].

CYP 3A4 is found in the mucosa of the small intestine and CYP 1A1 seen in the duodenum. Small amounts of CYP 2C8-10 and CYP 2D6 are available in the duodenum and jejunum. Cytochrome P450 isoenzymes have been distinguished all through the brain with high concentrations in the brain stem and cerebellum. These are believed to be vital in directing the concentrations of progesterone and corticosterone which assume a part in mood changes and sleep – awake cycles during stress, pregnancy and through the menstrual cycle [26].

Cytochrome P450 isoenzymes have been distinguished in the brush border of the proximal tubular cells and medulla of the kidney. They are involved in catalytic reactions including the arachidonic acid in the kidney leading to formation of eicosanoid products which have vasoactive properties and have impacts on ion transport, and thus influence the physiological components that control fluid volume and composition [27]. Type II pneumocytes in the lung contain cytochrome P450 isoenzymes but have a limited contribution to concentrations of CYP 19. Adipose tissue contains high concentrations of CYP 19 enzymes which are believed to be vital for the production of estrogens in the elderly.

BIOCHEMISTRY OF CYP450 ENZYMES

Every cytochrome P450 isoenzyme comprises of a solitary protein and one haeme group as the prosthetic moiety [28]. The haeme prosthetic group binds oxygen after electron transfer reactions from the reduced type of nicotinamide adenine dinucleotide phosphate (NADPH) and this response incorporates one particle of atomic oxygen into the substrate [29]. The reaction catalyzed by cytochrome P450, a mono-oxygenation, can be compressed as:

$$\text{NADPH} + \text{H}^+ + \text{O}_2 + \text{RH} \rightarrow \text{NADP}^+ + \text{H}_2\text{O} + \text{R} - \text{OH}$$

Where R represents to a substrate, for example, a steroid, unsaturated fat or compound with an alkenes, aromatic ring or heterocyclic ring substituent those serve as a site for oxygenation.

PHYSIOLOGICAL ROLE

It has turned out to be evident that the cytochrome P450 enzymes are associated with the biosynthesis as well as degradation of endogenous compounds, for example, steroid hormones, cholesterol and unsaturated fats [30]. These enzymes may have physiological roles in the brain, for example, signal transduction by arachidonic acid metabolites which are believed to be engaged with the release of peptide hormones from the hypothalamus and pituitary; the regulation of cerebral vascular tone by arachidonic acid metabolites; the regulation of progesterone and corticosteroids in the brain which are thought to have

an impact on mood and condition of excitement by interacting with GABA receptors; and the control of intracellular concentration of cholesterol which influence the transcription of low-density lipoprotein receptor and enzymes involved with cholesterol synthesis.

The CYP 2D6 enzymes direct the metabolism of neurotransmitters, for example, dopamine and serotonin and in this manner may have a part in deciding the psychological state and identity of individuals. Adrenal and gonadal steroid genesis is impacted by the enzymes CYP 11A, CYP 11B, CYP 17, CYP 19 and CYP 21 [31, 32]. CYP 19 assumes a vital part in estrogen biosynthesis in the gonads, mind, placenta and fat tissue. In the kidney, metabolites of arachidonic acid produced by renal cytochrome P450 upgrade NaKATPase and the Na.K.2Cl co-transporters bringing about diuresis and natriuresis. As an outcome of these impacts, the cytochrome P450 framework has a critical part in the reconciliation of body fluid volume and composition and consequently blood pressure control. In the liver, the biosynthesis of bile acids and endogenous steroids are carried out by CYP 7, 17, 19, 21 and 27. Bile acid synthesis from cholesterol can happen by two pathways, one started by CYP 7 (cholesterol 7 α -hydroxylase) in the liver and the other by CYP 27 (sterol 27-hydroxylase) which is a generally dispersed mitochondrial enzyme, notable in vascular endothelial cells [33]. Human CYP 2C8 enzyme found to be responsible for retinol and retinoic acid metabolism.

PHARMACOLOGICAL ROLE OF CYP450 ENZYMES

Drug Metabolism

Microsomal Enzymes

These are situated on the smooth endoplasmic reticulum (an arrangement of microtubules inside the cell), principally in liver, additionally in kidney, intestinal mucosa and lungs. The Monooxygenase, cytochrome P450, UGT's, epoxide hydrolyses are microsomal compounds. They catalyze the majority of the oxidation, reduction, hydrolysis and glucuronide conjugation. Microsomal enzymes are inducible by medications, food and different agents.

Non Microsomal Enzymes

These are available in the cytoplasm and mitochondria of hepatic cells and also in different tissues including plasma. The esterase, amidases, some flavoprotein oxidases and most conjugates are non microsomal. Reactions catalyzed are reduction, numerous hydrolytic reactions and all conjugation with the exception of glucuronidation. The non microsomal enzymes are not inducible but rather numerous show hereditary polymorphisms.

Both microsomal and non microsomal proteins are lacking in the infant, particularly premature, making them more susceptible to numerous medications, e.g.: chloramphenicol, opioids etc.

CYP450

The cytochrome P450 protein frameworks catalyze the metabolism of endogenous and exogenous compounds. The biotransformation of the endogenous and exogenous substrates renders these mixes hydrophilic or polar with the goal that they can be excreted. The reactions are gathered into stage 1 and 2 reactions. In stage 1 reaction oxidation or demethylation interceded by cytochrome P450 enzyme. The cytochrome P450 system catalyzes a wide assortment of reactions including epoxidation,

N-dealkylation, O-dealkylation, S-oxidation and hydroxylation of aliphatic and aromatic residues. Oxidation can bring about both activation and inactivation of a compound.

Like all enzymes, cytochrome P450 isoenzymes indicate saturable Michaelis – Menten energy and need co-factors for their action. Biotransformation inside the gastrointestinal tract is essential since it diminishes bioavailability after oral administration. Changes in the action of the cytochrome P450s is because of hereditary polymorphism, catalyst hindrance, enzyme induction and physiological factors. They might be induced or inhibited [34]. Figure 3 shows the mechanism of drug metabolism.

The mechanism of drug metabolism

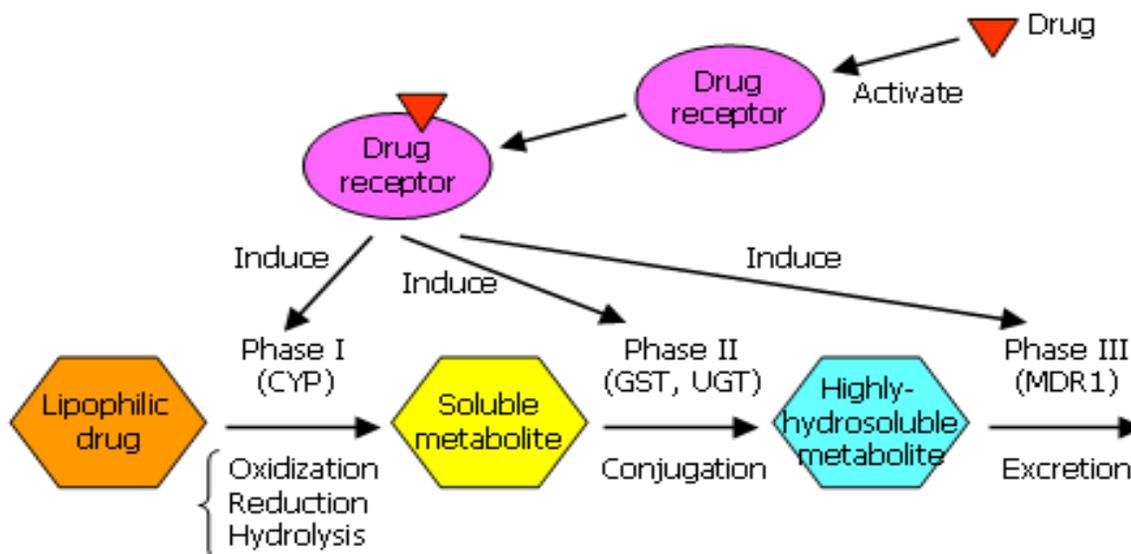


Fig 3: Mechanism of drug metabolism

ROLE OF CYP450 IN DRUG – DRUG INTERACTIONS

ENZYME INDUCTION

The impact of induction is essentially to expand the measure of P450 present and accelerate the oxidation and clearance of a medication [35]. It is fairly hard to foresee the time-course of enzyme induction in view of a few components, including the medication half-life and enzyme turnover, which decide the time-course of induction. A confusing factor is that the time-course of induction relies upon the time required for enzyme degradation and new enzyme generation. The short half-life of rifampicin brings about enzyme

induction (CYP 3A4, CYP 2C) evident in 24 h, though Phenobarbital, which has a half-existence of 3– 5 days, requires approximately 1 week for induction (CYP 3A4, CYP 1A2, CYP 2C) to become evident. These enzyme induction reactions likewise happen with smoking and long term liquor or medication utilization and can diminish the span of activity of a medication by expanding its metabolic disposal.

Presentation to natural contaminations and in addition extensive number of lipophilic medications can bring about induction of CYP enzymes. The most widely recognized system is transcriptional activation

prompting expanded synthesis of more CYP enzyme proteins. On the off chance that a medication activates its own particular metabolism, it is called auto induction just like the case with carbamazepine. In the event that induction is by different compounds it is called foreign induction. Metabolism of the influenced tranquilize is expanded prompting diminished intensity and term of medication impacts. On the off chance that the medication is a prodrug or it is used to a dynamic or harmful metabolite then the impact or danger is expanded. Understanding these components of enzyme induction and inhibition is critical to give proper various medication therapies [36, 37].

ENZYME INHIBITION

Inhibition is diminished enzyme activity because of direct interaction with a medication. These procedures more often starts with the initial dose of the inhibitor.

There are two types of enzyme inhibition. They are reversible inhibition and irreversible inhibition. Reversible inhibition are of three types i.e., competitive, non- competitive and uncompetitive. Clinical impacts are affected by these essential phenomenon's [38, 39]. The main sort is competitive inhibition amongst inhibitor and substrate for a similar restricting site on a enzyme. The size and adaptability of the coupling site of the microsomal P450 with which we are worried here are obscure. For instance, when single oral dose of metoprolol (50 mg), a beta-adrenoreceptor blocking agent and additionally propafenone (150 mg) were managed, or when the two medications were given in mix to healthy subjects, an around two-overlap lessening in the oral leeway of metoprolol was watched when propafenone was incorporated. The dose of metoprolol ought to be diminished when propafenone is additionally given [40].

Another is, non- competitive inhibition where the inhibitor binds at a site on the enzyme particular from the substrate, as occurs in traditional investigations of enzymology. Such illustrations incorporate interactions between cimetidine and enzymes. Cimetidine is bound to P450 and produces a stable cytochrome substrate complex. It is the formation of this boggling which anticipates access of different medications to the P450 framework. Cimetidine does not hinder conjugation mechanism including glucuronidation, sulphation, acetylation or deacetylation or ethanol dehydrogenation. It ties to the haeme part of P450 and is in this manner an inhibitor of phase I drug metabolizing reactions (i.e. hydroxylation, dealkylation). Albeit for the most part perceived as a nonspecific inhibitor of this sort of

metabolism, cimetidine demonstrates some level of specificity. Since each sub-atomic types of P450 have a haeme part, it is workable for cimetidine to nonspecifically inhibit any drug that is metabolized by any sub-atomic species [41, 42].

The degree of competitive or non- competitive for reversible inhibition is dictated by the relative binding constants of substrate and inhibitor for the enzyme and by the inhibitor's concentration. The basic factor for the "inhibition index" (the proportion of the characteristic leeway in presence of inhibitor to that without inhibitor), is the inhibitor's concentration in respect to its K_i value (K_i – inhibition constant determined in vitro). Along these lines, the most strong reversible 3A inhibitors including azoles antifungals and first generation HIV protease inhibitors have K_i value below 1 μM . Inhibition is phenomenal for compounds with K_i value >75 -100 μM .

The most specific CYP inhibitors fall into the classification known as mechanism based inhibitors. These medications are substrates for the target CYP and are changed over to reactive species that covalently bind to CYP isoenzymes prompting their inactivation. This kind of inhibition is known as irreversible or mechanism based or suicide inhibition. Many of 17 α -ethinyl substituted steroids e.g. ethinylestradiol, gestodene and levonorgestrel are accounted to cause mechanism based inhibition [43]. For irreversible inhibition the basic factor for inhibition is the aggregate sum as opposed to the convergence of the inhibitor to which CYP isozymes is exposed. Lipophilic and extensive sub-atomic size medications will probably cause inhibition. Two qualities make a medication susceptible to inhibitory interactions: one metabolite must record for >30 -40% metabolism of a medication and that metabolic pathway is catalyzed by solitary isoenzymes. Inhibitor will diminish the metabolism of substrate and promote drug effect and toxicity of the substrate. On the off chance that the medication is a prodrug then the effect is diminished. The procedure of inhibition more often begins with the first dose of the inhibitor and beginning and lasting of inhibition relates with the half-life of the medication involved [44].

ISOENZYMES AND DRUG INTERACTIONS

We know the individual isoenzymes engaged with the metabolism of vast number of essential medications. Induction or inhibition of these isoenzymes prompts clinically noteworthy medication interactions. Individual isoenzymes and their drug interactions are as per the following:

IA2: This is the main isoenzymes influenced by tobacco. Cigarette smoking may prompt triple

increment in 1A2 movement. Theophylline is processed to some degree by 1A2, which clarifies why smokers require higher dosages of theophylline than non-smokers [45]. Liquor represses metabolism of caffeine, a substrate of 1A2. Liquor has been accounted to cover the 1A2 initiating capability of smoking [46]. Presentation to polyaromatic hydrocarbons found in charbroiled substance can likewise actuate these isoenzymes. These isoenzymes additionally make metabolic initiation of procarcinogens cancer-causing agents e.g. aromatic and heterocyclic amines [47].

3A Isoenzymes: Members of the 3A subfamily are the most bounteous CYP compounds in the liver and record for around 30% of CYP enzymes in the liver. High levels are likewise present in the small intestinal epithelium and along these lines make it a noteworthy supporter of presystemic elimination of orally administered drugs. There is significant individual variability in hepatic and intestinal CYP 3A activity (about 5-10 overlap). Since 40-50% of medications utilized by humans include 3A mediated oxidation to some degree, the individuals from this subfamily are associated with numerous clinically imperative medication interactions. 3A4 is the major isoenzymes in the liver. 3A5 is also present in the kidneys [48]. An important interaction including induction of 3A is the diminishment in viability of oral contraceptives by rifampicin and rifabutin, in view of an induction of the 3A intervened metabolism of estradiol and norethisterone, the components of oral contraceptives [49].

2C9: CYP 2C9 makes up about 18% of the cytochrome P450 protein in liver microsomes (data only for antifungal). Some 100 therapeutic drugs are metabolized by CYP 2C9, including drugs with a narrow therapeutic index such as warfarin and phenytoin and other routinely prescribed drugs such as, tolbutamide, losartan, glipizide, and some nonsteroidal anti-inflammatory drugs. By contrast, the known extra hepatic CYP 2C9 often metabolizes important endogenous compound such as serotonin and, owing to its epoxygenase activity, various polyunsaturated fatty acids, converting these fatty acids to a wide range of biological active products [50].

2C19: This Isoenzyme additionally displays genetic polymorphism. It is associated with metabolism of various clinically critical medications e.g. omeprazole, diazepam, antidepressants and antimalarials [51]. It metabolizes arachidonic acid to various epoxyeicosatrienoic acids, linoleic acid to 9, 10-epoxy octadecaenoic acids and 12, 13-epoxy-octadecaenoic.

2D6: This isoenzymes represents to <5% of aggregate CYP proteins. It is likewise called

debrisoquine hydroxylase after the drug that prompted the revelation of its genetic insufficiency. Numerous psychotropic, antiarrhythmics and β – adrenergic receptor blocker drugs are substrates and also inhibitors of 2D6 [52].

2E1: This Isoenzyme is engaged with metabolism of low atomic weight toxins, fluorinated ether, volatile anesthetics and procarcinogens. This Isoenzyme is inducible by ethanol and is responsible to a limited extent for metabolism of acetaminophen. The metabolite of acetaminophen is profoundly reactive and hepatotoxic. Liquor dependant patients might be at expanded danger of acetaminophen hepatotoxicity due to 2E1 by alcohol [53].

ISOENZYMES ROLE IN DISEASE STATES

Changed action of certain isoenzymes has been embroiled in the advancement of tumor, adrenal hyperplasia and Parkinson's ailment. Smokers with expanded CYP 1A1 (aryl hydrocarbon hydroxylase) action are more inclined to creating lung growth. Hereditary contrasts in CYP 1A1 in people with a high danger of creating lung growth have been distinguished and people who are homozygous for a particular rare allele are at a more serious danger of building up the disease sickness [54].

The CYP 1B1 isoenzyme is elevated in patients with breast malignancy. As it is engaged with the metabolism of estrogens in the breast, it is recommended that it might have a part in the etiology of estrogen-dependent breast tumors.

The CYP 2D6 catalyst has been involved in intervening carcinogenesis by enacting procarcinogens in tobacco smoke prompting lung disease.

CYP 2E1 catalyzes the metabolism of aniline, chlorinated hydrocarbons and benzene, prompting the development of procarcinogens. It is recommended that genetic polymorphism of CYP 2E1 may assume a critical part in the advancement of hepatic cancer [55].

Reactive metabolites produced by synergist responses inside neuronal cells may cause neurotoxicity bringing about Parkinson's illness. Epidemiological examinations have demonstrated a pattern in which poor metabolizers of debrisoquine have a tendency to build up an early beginning of Parkinson's disease [56].

PHARMACOGENETICS AND DRUG RESPONSE

Pharmacogenetics can be defined as the science of determining the genetic differences on metabolic pathways which can affect individual responses to drugs, both therapeutically and adversely.

One out of each 15 white or dark people may have a misrepresented reaction to standard dosages of beta

blockers (e.g., metoprolol), or no reaction to the pain relieving tramadol. This is on account of drug metabolism by means of CYP450 enzyme displays hereditary changeability (polymorphism) that impacts a patient's reaction to a specific drug [57].

A particular quality encodes each CYP450 enzyme. Each individual acquires one hereditary allele from each parent. Alleles are alluded to as "wild type" or "variant," with wild type happening most normally in the overall population. An "extensive" (i.e., normal) metabolizers has got two duplicates of wild type alleles. Polymorphism happens when a variation allele replaces one or both wild type alleles. Variation alleles as a rule encode a CYP450 enzyme that has decreased or no movement. People with two duplicates of variation alleles are "poor" metabolizers, though those with one wild- type and one variation allele have decreased enzyme action. At long last, a few people acquire various duplicates of wild-type alleles, which brings about excessive enzyme action. This phenotype is named a "ultra rapid" metabolizers [58]. CYP450 enzyme polymorphism is responsible of observed varieties in tranquilize reaction among patients of contrasting ethnic origins. Change in drug reaction among people of various ethnic birthplaces likewise can be caused by hereditary varieties in other, drug metabolizing enzymes, drug transporters, and drug receptors. Figure-4 shows the different types of drug metabolizers.

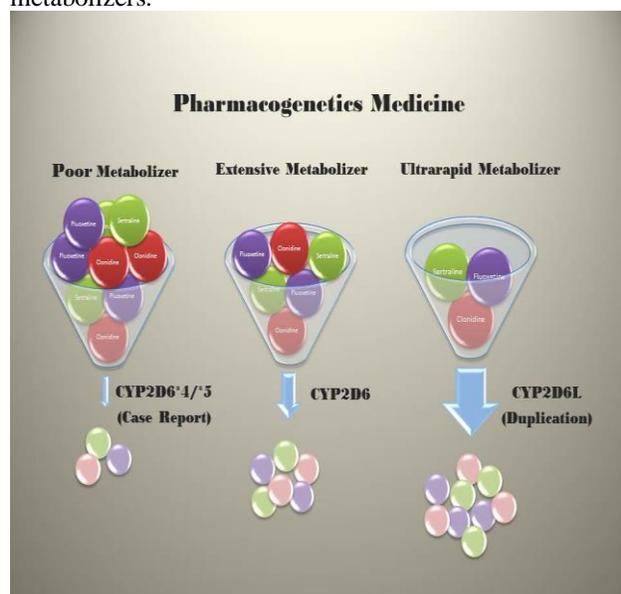


Fig 4: Types of drug metabolizers

As each isoenzyme is a particular gene product, hereditary varieties impact the statement of isoenzymes in various people and subsequently the limit of the person to utilize drugs. Hereditary polymorphism with clinical ramifications has been portrayed for 2D6, 2C19, 2C9 and 1A2. These

isoenzymes show polymorphism with number of allelic variations, the recurrence of which regularly changes between various populations. Around 5-10% of Caucasians and 1% of Asians are poor metabolizers of medications metabolized by 2D6. The recurrence of poor metabolizers in Indian population is around 2-4.8%. Poor metabolizers are more inclined to antagonistic medication responses since metabolism is diminished and blood levels are high. CYP 2D6 is engaged with O-demethylation of codeine to morphine. Henceforth poor metabolizers show hindered or no absence of pain after codeine administration. Polymorphism of 2D6 adds to the articulated intra individual fluctuation saw in the elimination of vital medications including tricyclic antidepressants, antipsychotics, mexiletine and a few β -adrenergic receptor blockers [59].

Around 5% of whites and 20% of Asians are poor metabolizers of medications metabolized by 2C19. The recurrence of poor metabolizers in Indian populace is around 11-20%. The Chinese are poor metabolizers of 2C19 and are more inclined to narcotic impact of diazepam and they are recommended for low doses of diazepam [60].

A region of developing interest is that identifying with results of inhibitory interactions of medications subjected to isoenzyme polymorphism. Dual medication treatment for annihilation of helicobacter pylori is more valuable in poor metabolizers of 2C19 than extensive metabolizers. This is a direct result of diminished metabolism of omeprazole in poor metabolizers and inhibition of omeprazole metabolism by clarithromycin [61].

Loss-of-function polymorphisms in CYP qualities shockingly regularly influence splicing and expression, as opposed to interpretation or protein structure. Gain-of-function variants incorporate copy number variants (CNV) with an expanded number of functional gene copies in CYP 2D6 and CYP 2A6 and also promoter variations (e.g. in CYP 2B6, CYP 2C19) and amino acids variants with expanded substrate turnover (e.g. in CYP 2B6, CYP 2C8). Shockingly couple of polymorphisms influences the substrate selectivity or the inducibility of medication metabolic pathways [62].

The clinical effect of polymorphism in a drug metabolizing enzymes must be considered in pharmacological context. Loss-of-function variants will prompt decreased clearance and expanded plasma concentrations, while Gain-of-function variants will prompt expanded leeway and lower drug concentrations. In the event that the medication is pharmacologically dynamic, this outcomes in expanded and diminished medication impact, individually, and possibly in sedate related harmfulness because of overdosing. In the event that

the medication is metabolically initiated (prodrug), the contrary is expected, and the pharmacological activity or toxicities of the metabolite(s) must be considered, as on account of CYP 2D6-dependent morphine formation from codeine.

CONCLUSION:

The cytochrome P450 isoenzymes are a super family of haemoprotein enzymes that catalyze the metabolism of a large number of endogenous and exogenous compounds. Recently, the cytochrome isoenzymes have been shown to be important in the synthesis of steroid hormones and bile acids, the arachidonic acid cascade and in central nervous function. These enzymes are a major determinant of the pharmacokinetic behavior of numerous drugs. Furthermore, alterations in cytochrome P450 activity have been implicated in some diseases.

The tremendous progress that has been made in understanding the drug metabolizing cytochrome P450 with respect to their functional properties and differences, regulation of gene expression, population variability, genotype–phenotype correlation, and clinical impact. Regulation of all CYPs is clearly multifactorial with sex, age, hormonal and disease states and inhibition or induction-type drug–drug interactions contributing to inter- and intra individual variability. Nevertheless, genomic markers have a confirmed impact on several CYPs, approximately in the order:

CYP 2D6 > CYP 2C19 ~ CYP 2A6 > CYP 2B6 > CYP 2C9 > CYP 3A4/5

By understanding the unique functions and characteristics of CYP enzymes, physicians may better anticipate and manage drug interactions. This practice will increase in future and will result in the formation of a rational information base that would indicate drug combinations to be avoided. For example inhibitors or inducers of 3A4 isoenzymes would not be given along with substrates of 3A4 and instead will receive alternative drugs that are not inhibitors or inducers of 3A4. This will improve rational drug use and facilitate better selection of drug combinations. Acquiring more knowledge on pharmacogenetics by the physicians and other health care professionals pave the pathway for personalized medicine.

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