Review Article

The Mosaic of Cytochromes Expression from Bacteria to Man

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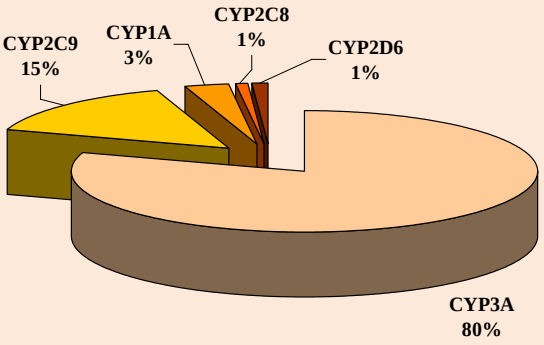
Abstract

Cytochromes are located in many different tissues of the human body. They are found in abundance on the intestinal and hepatic tissues in human and other living organisms. CYPs enzymes are metabolizing a large variety of xenobiotic substances. Activities of cytochromes P450 enzymes are influenced by a variety of factors, such as genus, environment, disease state, herbicides, alcohol consumption and herbal medications. However, diet and nutritional status seems to play the major role. The mechanisms of action of dietary chemicals, macro- and micronutrients on specific cytochrome P450 isozymes have been extensively studied. Cytochromes show a genetic polymorphism intra- or inter individual and intra- or interethnic. Moreover, effects of dietary modulation of the xenobiotic metabolism on chemical toxicity and carcinogenicity are stated. Bacteria have shown to have CYP -like genes. The tremendous metabolic capacity of the intestinal microbiota is associated to its enormous pool of CYP enzymes, which catalyzes reactions in phase I and phase II drug metabolism. Disease states, intestinal disturbances, ageing, environmental toxic effects, chemical exposures or nutrition modulate the microbial metabolism of a drug before absorption.



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Introduction

During the last decades, extended research in perinatal toxicology has gained the particular interest of many researchers all over the world and seems to be closely related to role of chemical hazards to human being. Chemically registered alterations of enzyme ontogenetic profiles, impairment in isoenzyme patterns, or perturbations to key metabolic pathways may end up in biochemical injuries in the absence of any known morphological or functional abnormality.

Moreover, those changes may have significant impact on human health and being closely related in maturation processes. Cytochrome *P*-450 (CYP450) is a large family of enzymatic proteins which catalyze the oxidation of substrates. Many endogenous compounds, as well as a large number of foreign compounds (xenobiotics), including drugs, are metabolized in the human body in many different sites by CYP450 through an oxidative transformation.

Cytochromes P450 (CYP) is a major source of variability in drug pharmacokinetics and response. They keep a critical role in the metabolism of xenobiotic compounds. Xenobiotics include commonly used medicines, which will be appropriately metabolized to varying degrees by the aid of cytochromes. Their catalyzing abilities are known for many chemical reactions such as hydroxylation, epoxidation, or heteroatom oxidation. Their endogenous function

includes biosynthesis of steroids, bile acids, and vitamin D3 and metabolism of fatty acids, prostaglandins, biogenic amines, and retinoids. Their exogenic function concerns drug metabolism and disposition.

Distribution

Cytochromes are located in many different tissues of the human body. However, research interest is mainly focused on intestinal and hepatic tissues due to their abundance to these sites. Intestinal and hepatic tissues are not mature in the newborn. Human intestine serves primarily as an absorptive organ for nutrients, although it has also the ability to metabolize drugs.

Living organisms such as plants, animals, bacteria, fungi, and humans possess P450 isoenzymes. A common progenitor gene seems to be the common ancestor of the superfamily due to the extensive similarity observed between CYP identified in man and bacteria date back to more than 3.5 billion years. A notably interesting theory states that the P450 xenobiotic-metabolizing enzymes were formed following a continuous survival combat between plants and animals [1, 2]. The evolutionary step seems to amalgamate plant to animal from around 2.3 or 2.4 billion years ago. Plants have to protect themselves from animal predators by synthesizing toxic metabolites. As result, animals have developed specific enzymes to compete against plant toxins as reported by Bezirtzoglou [3]. However, research on human cytochromes is limited comparing to the research performed on the cytochromes of other living organisms.

Early life and cytochromes

Indisputably, human newborns that happen to have diets low in iron or iron deficiency during the first year of life are associated with major perturbations that may insist on in spite of a subsequent iron reuptake [4–8]. Intrauterine growth hysteresis and diabetes mellitus during human gestation result in significant losses of fetal and neonatal brain iron. These failures in newborn health comprise a lower mental developmental index scores on the Bayley Scales of Infant Development and decreased reactivity and responsiveness to ordinary stimuli and communication capacity. This perinatal iron deficiency occurring in human newborns engenders important loss of CytOx (cytochrome *c* oxidase**)** activity in selected brain structures. CytOx is the iron-containing terminal enzyme in oxidative phosphorylation; its activity reflects neuronal metabolism. Specifically, the hippocampus and its prefrontal projections appear most impotent and therefore this finding is associated to the behavioral sequelae of perinatal iron deficiency [9].

Arguably, brain iron deficiency in the fetus or neonate could be more detrimental than postnatal iron deficiency because of the rapidity of brain growth during this critical developmental period [10]. Brain iron concentration peaks at birth and decreases through the weaning period, only to increase again during critical periods such as myelination [11]. Multiple hypotheses have been proposed around the role of brain iron in enzyme systems that regulate brain growth and maturity, after the processes of myelination and dopamine synthesis. Cytochrome *c* oxidase (CytOx) is involved in the last step of the oxidative phosphorylation reaction, as he keeps a critical role in the generation of ATP. Perinatal iron deficiency reduces neuronal metabolic activity, specifically targeting areas of the brain involved in memory processing [9].

Since 1950's researchers had successfully isolated and characterized various individual components of hepatic microsomes, which were reported to show an extensive metabolism of foreign compounds. After solubilization and resolution of the enzyme system into fractions containing different cytochromes such as cytochrome P450, NADPH cytochrome P450-Reductase.Moreover, a heat stable factor, subsequently shown to be phosphatidylcholine was isolated.

The major milestone of the above research is that the cytochromes exhibited the ability to have a catalytic activity towards a variety of drugs including antibacterials, anticoagulants, antidiabetic and nonsteroidal anti-inflammatory agents as well as steroid and fatty acid substrates and thus a new field of both pharmacological and functional studies was opened for further investigation. Actually, the knowledge that cytochrome P450 keep a major role upon hydroxylation reactions in adrenal cortex particles, as the "terminal oxidase" of the microsomal drug-metabolizing enzyme system is proven by Cooper et al [12].

Intestinal CYP Cytochromes

The intestine is exposed to potentially mutagenic substances from fetal development [13] to maturity. Several phase I and II enzymes are involved in tissue growth and ontogenesis. However, little evidence is given to age dependent changes of metabolic potential as well as their relationship to genotoxic injury in the intestine. Enzymes involved in xenobiotic transformation master phase I or phase II reactions [14]. Moreover, these enzymes are involved in tissue growth and development [13, 14].

The conversion of some xenobiotics to reactive electrophilic metabolites forming DNA and protein adducts in phase I, could induce toxic or tumor effects [15]. Phase I focuses on oxidations, reductions or hydrolysis reactions, while phase II lays on conjugation of the xenobiotic compound with a molecule [15]. The reduced hepatic metabolism following liver insufficiency or other liver disease states may be balanced to a certain extent by the presence of the CYP P450s in the intestinal and duodenal [16].

Specific receptors of the human gut such as nuclear receptors (NRs) or Toll-like receptors (TLRs) [17] are involved at the quorum-sensing between microorganisms of the intestinal microbiota and epithelial cells. However, as prerequisite for this communication role, the maturation and integrity of the intestinal epithelium is necessary for setting of the host innate response which also influences drug disposition and metabolism [3]. Disease and aging seem to be crucial upon the expression and activity of the intestinal CYP3A4 and other P450s enzymes [18, 19]. Duodenal, intestinal and gastric pH, intestinal transit time, gastric emptying time, P-glycoprotein, and bacterial colonization may influence drug absorption [20–21]. Differences in drug distribution could be explained by ageing which induce modifications of the circulating endogenous substances in plasma, total body fluids, extracellular water, fat, and protein concentration in plasma leading to another pattern of membrane permeability [18–20] and enterocytes maturation. Leaky gut syndromes are health disorders associated with increased intestinal permeability [22]. These syndromes account for a broad range of conditions, such as inflammatory or infectious bowel diseases, extended to cryptogenic skin conditions or other states [22].

It is known that the normal intestinal microflora plays an important role in host metabolism and provides a natural barrier against invading pathogens. Although the microbiota in humans and animals has been extensively studied, little is known of the changes that occur in the microbiota during intestinal maturation much less about the distribution and expression of CYP enzymes in human intestine. Changes in the intestinal digestive tract during development characterize transition to adult life [23]. The intestine is an important site of biotransformation and metabolic plant [3, 19–21]. However, information related to the developmental change of intestinal phase I and II xenobiotic metabolizing enzymes are scrimp.

Age dependent differences in xenobiotic enzyme expression [18–19], induction and DNA adduct formation throughout maturation were described upon rat intestine. Remarkable differences were observed between fetal and postnatal intestine, which could be influenced by maternal factors and the placental barrier, as well as tissue specific metabolism, the slighter differences produced during postnatal maturation of intestinal tissue. Physiological variation of metabolic competence and genotoxic injury could be causally related in the intestine. Age-dependent change of metabolic capacity and genotoxic injury in rat intestine [13]. In these terms, methylcholanthrene is a potent PAH carcinogen which may cross the placenta.

CYP and maturation of the intestinal tissue

Undoubtedly, as stated already phase I and II cytochrome P450 enzymes are implicated in tissue growth, development and ontogeny [24]. The inadequacy of perinatal glucuronidation is connected to the tissue maturation and growth [25]. During postnatal maturation of the intestinal tissue, minor differences of enzyme expression, induction and DNA adduct formation were observed. Physiological variation of metabolic dynamic and genotoxic lesion could be causally connected to the rat intestine [13].

Moreover, fractionation of rat small intestinal epithelial cells on the basis of their maturity has demonstrated high ratios of 12 S mtrRNA cytochrome b mt mRNA or 12 S mtrRNA /cytochrome oxidase I mt mRNA on the surface of the mature enterocytes. A gradual reduction in cytochromes numbers was observed towards the crypt immature enteroblasts [26]. As known, intestinal epithelial cells are derived from pluripotential stem cells near the base of the crypts, and differentiate as they move towards the luminal surface [27]. Yet, as the enterocytes migrate

towards the villus surface, the expression of the mitochondrial genome alters during cellular maturation in the intestinal epithelium. However, the understanding of the regulation of mitochondrial gene expression in developing and senescent cells is under investigation. Inveterate ulcers in adults have been related to the existence of aging cells in the damaged area, as senescence may verify the degree of tissue repair by inhibiting fibrosis.

Transforming growth factor-b (TGF-b) is a cytokine with a broad range of activities in tissue repair and a pleiotropic regulator of cell proliferation. It has been found that a long-term exposure to TGF-b provokes premature senescence in both fetal and adult skin fibroblasts. The mechanisms underlying this phenomenon are thorough studied [28]. Although the regulation of CYPs by inflammatory agents is extensively discussed. Changes in mRNA introducing changes in protein levels in response to the inflammatory stimuli are noted in rats. These changes may conduct increased toxicity or loss of efficacy of cytochromes targeting drugs [29]. Mere extensive studies were conducted in animal models, studies in humans seems to be tenuous.

Microbial lipopolysaccarides (LPS) of Gram(-) bacterial cells, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF), interferon gamma (IFN), transforming growth factor-beta (TGF) and interleukin-1 beta (IL-1) on expression of CYP2B6 and the CYP2C mRNAs in human hepatocytes were exposed to agents associated with inflammatory responses that were previously shown to regulate CYPs in rodents.

Cytochromes and inflammation

Data indicated that human hepatic cytochromes CYP 2C8, 2C9, 2C18, 2C19, 2B6, and 3A4 antiphons to inflammation are cytochrome –dependent regulated and thus may have a critical effect on human drug responses in disease states. In this vein, CYP2C18, is expressed at very low levels in liver tissue, and so it was unaffected by cytokine exposure. The response pattern of cytochromes CYP2C9 and CYP2C19 was proven identical as both cytochromes were down-regulated by IL-6 and TGF but not influenced by LPS, TNF, IFN, or IL-1 [30]. Data suggest strongly that, even with the overlapping effects of cytokines, human P450s are independently regulated in response to inflammation and infection [30].

However, the differentiation in inflammatory response to cytokines may be crucial for patient treatment, since it estimates that CYPs are presumable to be distinctly regulated at different stages and by various mechanisms, as result to inflammatory attack or disease. This foreknowledge is enhanced by the differential sensitivity of CYP-dependent clearance observed in infectious liver disease [31].

Cytochromes activity upon germ - free animals

Premature infants are susceptible to intestinal ischemia during the newborn period when their intestinal tracts are functionally and structurally immature. Studies have shown that exogenous glucocorticoids speeds the intestinal maturation [32]. A germ-free or axenic animal harbor no living forms as it is deprived from bacteria constituting the normal microbiota and thus, resembles to an extent the premature infant profile but mainly the caesarian section sterile newborn [33]. Those animals are elevated in sterile isolators feed on sterile foods. On a pilot basis, isolators have been used in several hospitals for the care of patients with extensive burns, as well as immunocompromised persons [34].

The small intestine of germ-free animals differs from the conventional in considerable features. The intestinal wall germ-free animal's is thinner. The intestinal villi and the lamina propria of germ-free animals are thinner and atrophic compared to those of conventional animals; Peyer's patches are smaller in size. The amount of mucosal layer is much more important. Moreover, histological examination of the lamina propria encounters few lymphocytes and macrophages as an exposure to microbial antigens is missing.

The mitotic count in crypt cells of the intestine is lower and the time taken to migrate to the villous edge is much longer as in conventional animals. A special feature of germ-free animals is the possession of an inflated caecum due to the enhanced water transport following restitution of the Cl- concentration. This fact constitutes the main cause of death in germ-free animals, as their intestine pops due to the imprisonment of large amount of water.

Profound expression (10-fold) of the Ntrk2 gene encoding the neurotrophic tyrosine receptor kinase 2 TrkB in conventional mice was observed. Neurotrophins are growth factors that promote survival in development and maintenance of neurons. In the brain, breaking up of these molecules has also been shown to have cognitive effects such as hyperactivity, increased anxiety and increased locomotive activity [35].

The influence of immunoregulating humoral thymus factor T-activin (fraction AFT-6) on the activity of xenobiotic metabolism enzymes and cellular-dependent cytotoxicity was investigated in germ-free animals. T-activin stimulated cytochrome P-450, NADP-cytochrome-C-reductase, glutathione-S-transferase, benzopyrene hydroxylase and epoxyhydrase activity [36].

Cytochromes and nutrition

It is known that dietary substrates influence the levels and activities of P450 isoenzymes in various stages. Specifically those dietary components could affect the levels of P450 by acting upon the following processes:

1. Transcription of specific P450 genes,
2. Degradation of specific mRNA,
3. Translation process, and
4. P450 cytochromes degradation through protein bending or by auto-inhibition [37, 38].

Many dietary chemicals are substrates of the P450-dependent monooxygenase system. They or their metabolites may inhibit or enhance the activities of this system by binding to P450 species or to NADPH: P450 reductase, by affecting the interaction between these enzymes, or by affecting key steps in the catalytic cycle.

The development of hydrolase activity in the intestinal brush border membrane is important for the maturation of digestive function in early life. Hydrolase activity is induced by cytochromes P450. Hydrolases are found in form of membrane-bound proteins on the endoplasmic reticulum as well as in soluble forms in the cytosol of the cells. The membrane-bound hydrolase form carries a sequence of 20 amino-acids at the N-terminal which is attached to the intestinal membrane keeping its active site out of the membrane. The activity of this microsomal enzyme is shown low during the early life and increase with ageing due to the intestinal maturation. Moreover, it seems to be a gender dependent activity as males have usually twice the activity of females. Nutrition seems to carry a capital role to these matters [39].

Foods are composed of multiple chemical components which could have the ability to inhibit or induce the activity of drug-metabolizing enzymes .The levels and activities of cytochrome P450 enzymes are influenced by a variety of factors, including the diet. Dietary components have remarkable influences on the metabolism of drugs, environmental chemicals, and various endogenous substrates. On the side, dietary effects upon metabolism of exogenous substrates may alter the therapeutic impact of a drug.

In order to evaluate a possible role of the intestinal microflora in the metabolism of the highly mutagenic compounds formed in fried meat, conventional and germfree male rats were fed a semi-synthetic diet containing fried meat [40]. Measurement in microsomes from the small intestine and the liver showed that the excreted mutagenicity was significantly higher up for the conventional animals, as an obtained result of a more important fecal excretion of mutagens in those animals. It is then understood able that the excretion pattern and the metabolism of the different compounds present in fried meat are affected by the germfree status. Feeding cholesterol and bile acids to conventional and germ-free rats affects microsomal enzyme activities involved with the metabolism of such steroids. The most consistent effects, particularly on hydroxylases, were found with cholesterol, which may be a regulator of microsomal enzyme activities.

Grapefruit juice acts by inhibiting presystemic drug metabolism mediated by CYP3A isoforms in the small bowel. Thus, grapefruit juice could markedly increase the oral bioavailability of a number of drugs, as felodipine, cyclosporine and other [41, 42]. Medicines having low oral bioavailability because of substantial presystemic metabolism mediated by CYP3A4 appears influenced by grapefruit juice. Although research works exalt the flavonoid, naringin, or the furanocoumarin, 6′,7′-dihydroxybergamottin, as being active components by inhibiting drug oxidative metabolism microsomes by naturally occurring flavonoids [43]. However, it has been drawn in

that only intestinal CYP3A4 is inhibited by the grapefruit juice, while liver resident cytochromes CYP3A4 enzymes are not affected. It is also noteworthy that multiple adverse effects are observed upon combination of grapefruit juice with cisapride or artemizole. It is then of essential importance for a patient before dispensing a medicine to be aware by his doctor and pharmacist for this food–drug interaction which could be harmful for his life by altering drug availability.

It seems that orange and grapefruit juice interacts with felodipine by a similar mechanism focusing on the inactivation of the intestinal CYP3A4. However, the lack of interaction between orange juice and cyclosporine arguments that grapefruit juice may also inhibit the intestinal P-glycoprotein, whereas orange juice may selectively acts upon intestinal cytochromes CYP3A4 [44]. A component of garlic oil, which is the diallylsulfide has been shown to induce rat hepatic cytochromes P450 2B1 based on the increase of immunodetectable protein and pentoxyresorufindealkylase activity [45]. Compared with the effects of nonnutritive dietary chemicals, the effects of macronutrients on drug metabolism are not yet completely elucidated.

Diets with low protein content or low quality proteins usually result in lower rates of xenobiotic metabolism than a normal diet. Low fat diet to rats caused an increase in the microsomal metabolism of various substrates, including aminopyrine, ethyl morphine, hexobarbital, heptachlor, BP, NDMA, phenobarbital and anilin. Fat amounts seems to keep a key role in affecting P450 levels, and those rich in polyunsaturated fatty acids are more effective than those rich in saturated and monounsaturated fatty acids[46].Fasting can be crucial in raising P450 E1levels in persons under regime for weight loss which showed an enhanced toxicity of acetaminophen.

The induction of cytochromes P450 2E1 by fasting can account for the increased aniline hydroxylase and NDMA demethylase activities. Fasting for 2 or 3 days caused a 50% decrease in the level of the male-specific P450 2C11 [47]. Caffeine metabolism occurs primarily in the liver, where the activity of the cytochrome P450 isoform CYP1A2 encounters for almost 95% of the primary metabolism of caffeine. In this vein, caffeine pharmacokinetics may be altered by drugs acting upon the activity of CYP1A2 as it is the case of therapeutic schemes with certain antidepressants or neuroleptics. Therefore, patients taking caffeine medicines or coffee drinkers necessity dosages adjustment for a proper treatment.

The effects of micronutrients such as vitamins on drug metabolism have been studied extensively [49].Results seems to be controversial, as pronounced vitamin deficiencies seems to correlate with decreased metabolic functions and lowered levels of P450-dependent metabolic activities in contrast to mild deficiency in a nutrient which may enhance P450-dependent activities. Thus, the degree of deficiency sets the resulting metabolic effects due to the variable effects on specific P450 isoenzymes [50].

Thiamin deficiency increased the hepatic microsomal P450 2E1 level but not the P450 2Cll level. Thiamin deficiency was shown to increase cytosolic glutathione S-transferase activity moderately but not steroid isomerase activity [51]. More research must be set in this direction in order to provide a response to this complex issue.

Environmental and other factors and CYP enzymes activity

Environmental factors, sex, ethnic differences and nutrition are playing a catalytic role in the inducibility of the hydrolase. It is reported that expression and inducibility of CYP enzymes in cultured hepatocytes is influenced by the gender, age, or ethnicity of the donor in the frame of a multiethnic study limited to Caucasians, African Americans, and Hispanics [52].

Specifically, when compared Caucasians and African Americans towards liver microsomes from Hispanic population; these latter seems to have about twice the average activity of CYP2A6, CYP2B6, and CYP2C8 and half the activity of CYP1A2. Flavonoids such as, myricetin, isorhamnetin, and quercetin may affect the activities of porcine CYP1A, CYP3A, and CYP2E1 in a gender-dependent manner [53].

Cytochrome P450f is developmentally expressed in both male and female rat liver. Cytochrome P450f levels amounts from ~ 1% in young animals to approximately 7 and 14% of total cytochrome P450 in the adult male and female rats respectively. However, the cytochrome P450g seem to be sex depended since it is expressed and developmentally regulated only in male rats liver where its levels of cytochrome range from 1% in 3-week-old male rats to 17% of total cytochrome P450 in 6-week-old adult animals[54].

Despite the above formulation, other authors demonstrate a negative relation between age and total P450 content, NADPH-cytochrome c reductase activity and the levels of CYP 2E1 and CYP 3A proteins . CYP 1A2 and CYP 2C proteins were unchanged with advancing age. Moreover, these same authors stated that gender did not influence the expression of any of the CYP proteins [55]. Summarizing up, age but not gender seems to be a constitutional factor that influences the hepatic content of cytochrome P450 and some other CYP proteins.

Brusque smoking cessation can affect the metabolism of drugs. Cigarette smoking seems to be associated with high levels of CYP 1A2 and CYP 2B6. Smoking deprivation accrues the risk of cross drug reactions, stating the increased toxicity from clozapine and olanzapine. However, replacement nicotine therapy does not influence the CYP1A2 activity [56].

It is noteworthy that genes of the cytochrome CYP1A1 and CYP1B1 as well as aldo-keto reductases AKR1C1, AKR1C3 and AKR1B10 families were highly expressed (15- to 30-fold) in oral squamous cell carcinoma (OSCC) [57]. CYP2E1 play a key role in the biodegradation of a number of environmental carcinogens, thus this CYP enzyme seems to be strong related to neoplasia's. Particularly, polymorphisms of CYP2E1 and oesophageal and gastric cancer were observed in the Chinese population [58]. Psychotropic and antidepressant medications, generally metabolized by the liver, can suspend the liver's cytochrome P450 enzyme system (CYPs 3A4, 1A2, 2C9, 2C19 and 2D6) [3]. These plasma level changes may result in reduced or increased efficacy of a xenobiotic drug. Carbamazepine is a powerful inducer of CYP3A and comprises some other drugs effectiveness.

Alcohol induces at least 3A4 and 2E1. Concerning CYP2E1, it is believed that it may be a key factor in the pathogenesis of alcoholic liver disease [59]. Alcohol excess was associated with decreased cytochrome P-450 content and AHH activity [60]. Ethanol can affect the absorption, plasma protein binding and distribution of xenobiotics as well as have profound influence on phase I and phase II metabolism of xenobiotics in both animals and humans [61, 62].It is known that chronic administration of ethanol increases the metabolic clearance of various drugs such as meprobamate, pentobarbital, aminopyrine, tolbutamide, propranolol, rifampicin, and testosterone. Moreover, ethanol could affect the carcinogen metabolism in the liver by having dual effects. Ethanol suspends hepatocarcinogenesis of NDMA while increased tumorigenesis in the nasal cavity is observed [63]. Environment plays an important role in cytochromes induction [64].

Induction of liver microsomal cytochrome P450E in fishes from Bermuda islands is associated to contaminant residues and chemicals .It is then proposed the introduction of P450 induction as an indicator of chemical contamination in aquatic systems [65]. However, the exact pharmacokinetic mechanism of CYP2E1 induction is not fully investigated, although the enzyme is clearly correlated to both alcohol and nicotine as well as the higher ethanol elimination rates among smokers [66].

Hypericum perforatum L. (St. John's wort, SJW), a common herbal medication in USA,may induce or inhibit some hepatic enzymes. It is reported that SJW accrues the activity of cytochrome CYP3A4 enzyme while it reduces plasma concentrations of certain drugs. Hyperfor in treatment induced enzymatic activity of CYP3A4 and CYP2C9 was observed, but no impact upon CYP1A2 or CYP2D6 enzymes [67]. Drug interactions depend on a variety of factors such as dose, frequency and timing intake, dosing regimen, route of drug administration and therapeutic range.

As stated previously, most psychotropics and other medicines are metabolizable in liver. Therapeutic effect requires a minimum plasma concentration of the psychotropic drug. However, hepatic enzyme induction can result in sub-therapeutic plasma levels and alter the drug efficacy. Summarizing, the systematic pharmacokinetic monitoring of patient's plasma levels is required in order to adjust the prescribed medicine levels.

CYP 450 plays an important role in the pathogenesis of the cardiac hypertrophy. It was demonstrated that following exposure to benzopyrene, a cardiac hypertrophy is observed by altering arachidonic acid metabolism through the induction of the expression of CYP -hydroxylases and soluble epoxide hydrolase enzymes. Exposure to benzopyrene occurs in polluted aerial or aquatic environments, from cigarette smoke, smoked consumed foods, during forest fires or incineration procedures as polycyclic aromatic hydrocarbons are produced. These last were correlated with the presence of cardiovascular diseases [68]. Unlike, a cardioprotective effect is demonstrated when epoxide hydrolase enzymes inhibitors are present. Remarkable increase in metabolism of metoprolol is induced by CYP2D6 during pregnancy [69].

Mechanisms affecting drug metabolism

Drug interaction mechanisms involving the CYP enzymes are classified as either CYP enzyme inhibition or CYP enzyme induction. The inhibition of CYP450 enzymes is described to be a slow regulatory process at the transcriptional level. In contrast, CYP450 induction consists of a rapid CYP450 enzyme activity of the in taken drug. This should result in inefficient therapy as drug concentration is altered and probably a life-threatening situation [70]. Enzyme inhibition occurs when 2 drugs compete for the same enzyme receptor for their metabolism .The more puissant inhibitor will outbalance and it will be produced decreased metabolism of the competing drug. This metabolic decrease could be related either to increased serum levels of the non metabolized drug by leading to toxicity or simply decreased efficacy of the drug. Identifying the extent of the drugs connected to act as enzyme substrates, inducers, or inhibitors, we could prevent from multiple drug interactions and effects by adjusting the patient's drug prescription or avoid co-administration.

Moreover, taking in account that multiple dietary factors can modulate P450 E1, the question is raised whether a higher or lower level of this enzyme, as well as the presence of other cytochromes is more beneficial and salutary to health. As P450 E1 is involved in lipid peroxidation, the question arises if oxidative stress could be associated to the important levels of P450 E1 [38]. In this vein, it should important to pump knowledge on the involved mechanisms which could affect a drug metabolism in association to a specific food or dietary substrate. The following theories seem to be retained on this issue:

- xenobiotic dietary compound reacts, sequesters or binds with the drug
- xenobiotic dietary compound modifies drug absorption or uptake.
- xenobiotic dietary compound affects Phase I and Phase II metabolism
- xenobiotic dietary compound binds to plasma proteins

Most known pathways of CYP P40 drug metabolism isoenzymes are reported on **Tables 1–3**. However, we must report that some drugs are metabolized by more than one isoenzyme, as they possess a dual pathway of metabolism. Nutritional factors, such as proteins, carbohydrates, fats, vitamins, minerals, affect the efficiency of these reactions [71]. As discussed previously, diets low in protein, fatty acids, vitamin and mineral deficiencies and low caloric can affect the cytochromes P-450 and their activity toward multiple drugs [72].

Table 1 Substrates of isoenzymes P450 drug metabolism

P450 isoenzymes	SUBSTRATES OF ISOENZYME
CYP1A2	caffeine, theophylline, theobromine, paraxanthine, clozapine, fluxosamine, imipramine, pimozide, propanolol, tacrine, warfarin
CYP2C9	Rifampicin, amitryptiline, diclofenac, hyperforin, Phenobarbital, ibuprofen, naproxen, piroxicam, phenytoin, warfarin, tolbutamide
CYP2C19	tamoxifen, amitriptyline, clomipramine, diazepam, cyclophosphamide, omeprazole, imipramine, phenytoin
CYP2D6	metoprolol, amitriptyline, nortryptiline, timolol, codeine, dectromethrophan, desipramine, imipramine, tramadol
CYP2E1	ethanol, carbon tetrachloride, acetaminophen, benzene, nitrosamines, azo, dapsone, chlorzoxazone, isoniazid, halothane
CYP3A4	alfuzosin, colchisine, alprazolam, astemizole, calcium chanel blockers, carbamazepine, cyclosporine, doxorubicin, erythromycin, dexamethasone, felodipine, HIV protease inhibitors, disopyramide, ergotamine, lovastatin, fluticasone, methylprednisolone, nifedipine, quinidine, quinine, tacrolimus, triazolam, repaglinide, rifabutin, sildenafil, tadalafil, vardenafil, vinblastine, vincristine

Table 2 Inhibitors of isoenzymes P450 drug metabolism

P450 isoenzymes	INHIBITORS OF ISOENZYME
CYP1A2	cimetidine, ciprofloxacin, erythromycin, citalopram, diltiazem, fluvoxamine, ofloxacin, tacrine, mexiletine, ticlopidine
CYP2C9	fluconazole, fluoxetine, isoniazid, metronidazole, paroxetine, sulphomethoxazole/trimethoprim, ticlodipine, sulphaphenazole, phenylbutazone
CYP2C19	cimetidine, fluvoxamine, fluoxetine, ticlopidine, ketoconazole, paroxetine, omeprazole, lansoprazole
CYP2D6	chlorpheniramine, fluoxetine, indinavir, haloperidol, quinidine, ritonavir, paroxetine, propafenone, thioridazine, ticlopidine
CYP2E1	water cress, disulfiram
CYP3A4	cimetidine, cyclosporine, diltiazem, fluconazole, HIV protease inhibitors, ketoconazole, most macrolides, miconazole, omeprazole, quinidine, itraconazole, verapamil, ritonavir, grapefruit juice

Table 3 Inducers of isoenzymes P450 drug metabolism

P450 isoenzymes	INDUCERS OF ISOENZYME
CYP1A2	carbamazepine,tobacco
CYP2C9	rifampicin,secobarbital,Phenobarbital,
CYP2C19	norethindrome,carbamazepine
CYP2D6	dexamethasone,rifampicin
CYP2E1	isoniazid,tobacco,alcool
CYP3A4	ritonavir,rifabutin,rifampin,carbamazepine

Disease states and cytochromes

Foods and diet keep a capital role in drug metabolism. As stated previously, grapefruit juice suspend the oxidation of nifedipine and felodipine in human volunteers, as it is rich in quercitin and naringenin, which in their turn inhibit P450 3A4, responsible for the metabolism of the dihydropyridine drugs .Moreover, P450 3A4 is associated to aflatoxin B1 activation in humans. It is assumed that consumption of grape fruit juice by inhibiting aflatoxin B1 activation should without doubt play an important role by inhibiting hepatocarcinogenesis in exposed individuals [73].

A divergent effect is observed in the case of cruciferous vegetables (*Cruciferae*, renamed as *Brassicaceae*) consumption, such as broccoli, cauliflower, Brussels sprouts, cabbage, radish. In one hand, an anti-cancer protective effect of cruciferous vegetables has been related to their capacity to induce phase II enzymes. On the other hand, cruciferous vegetables induce cytochrome P4501A2, which is reported to catalyze the metabolic activation of various procarcinogens, including aromatic amines in tobacco. Thus, frequent intake of cruciferous vegetables could also result in cancer-enhancing effects [74]. Indoles and isothiocyanates are found in cruciferous vegetables are reported to inhibit carcinogenesis experimentally in animals and this effect must be associated to the induction of the intestinal

cytochrome P450 1A1 which may contribute to metabolization and elimination processes of the dietary polyaromatic cancerigenic hydrocarbons [75].

As stated previously, indoles inhibit carcinogenesis. In these terms, indole-3-carbinol incorporated into a consumed food increases the estradiol2-hydroxylase activity in rats and humans [76] possibly associated to the induction of cytochromes enzymes P450 1A1 and P4501A2. Dietary effects upon drug metabolism seems to be associated to the induction of the different cytochromes, as food-drug interactions have been reported to occur in various systems in the body. Metabolic food-drug interactions occur when a certain food effects upon the activity of a drug-metabolizing enzyme, resulting to a modification of the pharmacokinetic processes of drugs metabolized by this enzyme. However, this effect must be more closely associated to the intestinal cytochromes as they participate tightly on the profile of the intestinal microenvironment exposed to the ingested food.

It is then essential to have extended knowledge upon the qualitative and quantitative profile of the chemicals for developing possible harmful effects. Specifically, the requirement of the drug dose adjustment to maintain its concentration within the therapeutic windows [77].

It is reported that depending on the dose, a compound can develop beneficial or harmful effects. However, most of the described studies were carried in animals, such as rats and mice. Thus extended research is needed to clarify this issue of the mechanisms related to food and cytochrome enzyme profile by extrapolating experimentation to humans.

Glyphosate, is the major active ingredient in Roundup®, which is a popular herbicide used worldwide. Unfortunately, remnants of this drastic substance are found in foods, such as primarily of sugar, wheat, corn and soy. Glyphosate is inhibited by cytochrome P450 enzymes and seems to develop toxicity to mammals, albeit confirmation from the producing industry about its innocuity. As mentioned, CYP enzymes play crucial roles in drug metabolism by detoxifying xenobiotics. Glyphosate is reported to enhance the harmful effects of food chemical residues and environmental toxins.

Cytochrome CYP enzymes acts synergistically to the disruption of the biosynthesis of aromatic amino acids by gut bacteria having as result different disease states such as various intestinal disorders, autism, obesity, cancer.

The case of autism is somewhat interesting are recent research is oriented to this issue. It is now well documented that autism is associated with dysbiosis in the gut [78].

The hypothesis that autism might be related to metabolic dysfunctions is produced. The impotence to metabolize phenolic amines which are toxic for the CNS could aggravate autistic disease [79]. Autism, depression, dementia, anxiety disorder and Parkinson's disease and some other neurological status are associated with abnormal sleep patterns, which are directly linked to pineal gland dysfunction. The pineal gland is highly susceptible to environmental toxicants. Environmental pollutants, such as aluminium and glyphosate, the latter being the active ingredient in the herbicide (Roundup), disorganize the cytochrome P450 enzymes, which are involved in melatonin metabolism [80]. Moreover, melatonin synthesis derived from tryptophan in plants and microbes is suspended by glyphosate [80]. All living organisms such as plants, animals, bacteria, fungi, and humans carry P450 isoenzymes. In humans, more than 74 CYP genes and 33 pseudogenes arranged into 18 families and 42 subfamilies have been found [81, 82].

Microbial colonization or infection of the bowel can considerably modify cellular and humoral immunity of the intestinal system during normal development. Understanding of the microbial-host gut mucosal interactions and their consequences may require new or alternative approaches to therapeutic schemes.

Metabolic potential of the intestinal microbiota

Microbial microbiota metabolism is known to participate in metabolic activation or detoxification of the exogenous compounds. Several of these compounds are absorbed and conjugated in the liver .Intestinal enzymes expedite their effective resorption after being excreted in the bile. The intestinal microbiota interacts extensively with the host through multiple metabolic exchanges and might be involved in human disease. Intestinal cytochromes P450 layered on the intestine provide the principal source of biotransformation of ingested xenobiotics.

Albeit its main role in toxifying or detoxifying xenobiotics, high intestinal cytochrome P450 levels have been correlated to the gastrointestinal cancer as the intestinal metabolism of trifluoroethanol predispose to intestinal ulcers

followed by systemic bacterial infection and probable colorectal cancer [83]. Pronounced changes in intestinal microflora of conventional or germfree animals are associated to induction or repression of certain isoforms of P450s [84]. The reported high metabolic capacity of the intestinal flora seems to be based on its enormous pool of enzymes [1] that catalyze reactions in phase I [85, 86] and phase II [87].

In this vein, research is focused to the enzymatic activity of the intestinal microflora in relation to the presence of cytochrome P450s enzymes in the major bacterial strains coming from the human fecal flora [88]. Specifically, intestinal *Eubacterium aerofaciens* has shown to have a CYP -like gene [88]. *Desulfomonas pigra* isolated from human feces was found to carry a cytochrome c and a desulfoviridin-like pigment [89]. Moreover, the genome of *Streptomyces coelicolor* A3 [2] revealed 18 cytosolic CYPs with six ferredoxin proteins and two soluble ferredoxin reductases [90, 91].

Another striking observation carry the PAR bZip Dbp, Tef and Hlf genes which are expressed at important levels in germ –free animals and are stated to play a capital role in circadian rhythm and xenobiotic metabolism [92]. The circadian PAR-domain basic leucine zipper transcription factors DBP, TEF, and HLF modulate basal and inducible xenobiotic detoxification [93]. In the circadian cycle regulation and the xenobiotic metabolism, the aryl hydrocarbon receptor nuclear translocator like (arntl or BMAL1) is involved, which permits a 7 times lower expression in germ-free animals [94]. Circadian sensitivity to the chemotherapeutic agent cyclophosphamide depends on the functional status of the CLOCK/BMAL1 transactivation complex. It is then expected that intestinal microbiota may play an important role upon the regulation of the peripheral circadian rhythm of xenobiotic metabolism [94].

Bile acids and steroids participate in the reduction of microsomal metabolism following microbial colonization of the adult germ-free animal, compared to the levels of conventional animals which need longer time, more than six weeks [95]. Thus, a correlation between xenobiotic metabolizing impact and longevity seems to be real. Presumably, the lack of intestinal bacteria in germ-free animals leads to excess amounts and accumulation of the nuclear receptor CAR-ligands such as bilirubin, bile acids and steroid hormones. This will asserts CAR target genes active and ensures an efficient swift of the xenobiotic metabolism [96].

Table 4 Functionality of bacterial P450 (CYP)

Systematic name	Bacterial species	Trivial name	Functionality
CYP101	*P.putida*	cam	Camphor 5-exo hydroxylation
CYP102	*B.megaterium*	BM-3	Fatty acids; pentadecanoic and palmitic acids ω2 hydroxylation
CYP103	*Agrobacterium tumefaciens*	PinF1	Plant inductible
CYP104	*A.tumefaciens*	PinF2	Plant inductible
CYP105A1	*S.griseus*	SU1	Sulphonyl urea oxidation
CYP105B1	*S.griseus*	SU2	Sulphonyl urea oxidation
CYP105C1	*Streptomyces*	ChoP	Cholesterol metabolism
CYP105D1	*S.griseus*	SoyC	Xenobiotic trasformation
CYP106	*B.megaterium*	meg	Fatty acid and steroid oxidations
CYP107A1	*S.erythraea*	eryF	Erythromycin biosynthesis
CYP107B1	*S.erythraea*	ORF405	6-deoxyerythronolide B C-6 hydroxylation
CYP108	*Pseudomonas. spp.*	terp	terpα-Terpineol 4-methyl hydroxylation
CYP109	*B.subtilis*	ORF405	Oxidation
CYP110	*Anabaena spp (Cyanobacter)*	ana	Oxidation
CYP111	*P.incognita*	lin	8-methyl hydroxylation of linalool

CYP112	*Bradyrhizobium japonicum*	BJ-1	Nitrogen fixation activation
CYP113	*Sacc.erythraea*	eryK	Erythromycin 12-hydroxylation
CYP114	*B.japonicum*	BJ-4	Tylosin biosynthesis and other functions
CYP153	*Acinetobacter sp.*	Alk	Hydroxilation n-alkanes
CYP154	*Streptomyces coelicolor*	A3(2)	Narbomycin /Pikromycin formation
CYP154	*Streptomyces venezuelae*	YC-17	Neomethylmycin formation

CYP and liver expression profile

Furthermore, gut microbiota was connected with liver genes expression profiles. It seems that a number of 112 categories of different expressed genes are involved in the xenobiotic metabolism [97]. Thus, we focus our discussion on key genes reported to have important liver functions. Bacterial enzymes able to hydroxylate steroids have been listed. The cytochrome CYP154C5 from *Nocardia farcinica* IFM 10152 which is a bacterial P450 monooxygenase, constitutes a promising catalyst as it has the potential to convert testosterone to 16α-hydroxytestosterone. We can presume that his enzyme is an important precursor for the synthesis of high value steroidal drugs in the pharmaceutical industry due to its high regio and stereoselectivity in the hydroxylation of many different steroids [98].A special point of interest is attained for a group of genes influenced by the same xenobiotic regulator: the NR CAR. CAR was considerably expressed in the liver of germ-free animals in the absence of any intestinal microbiota. Yet, the CAR-regulated gene POR is coding for the P450 oxidoreductase. Moreover, it is known that levels of bile acids, steroid hormones and bilirubin are regulated by gut microbiota and thus, germ –free animals produce reduced fecal secretion of bile acids and neutral steroids and increased levels of cholesterol in the liver and serum [99].

Microbial CYP enzymes

Bacterial P450s form a large proportion of the superfamily P450 [3].They are structurally characterized by using X-ray crystallography. The most extensively studied bacterial P450s are the CYP101from *Pseudomonas putida* involved in Camphor 5-exo hydroxylation and the CYP102 from *Bacillus megaterium* in fatty acid ω-2 hydroxylation.

Other cytochromes P450s are present in bacteria, as CYP107 from *S.erythraea* functioning upon erythrosine biosynthesis, CYP108from *Pseudomonas spp.* implicated in α-Terpineol 4-methyl hydroxylation, CYP119 from *Sulfolobussol fataricus* functioning in different antibiotic biosynthesis and CYP154 from *Streptomyces coelicolor* in tylosin biosynthesis (**Table 4**).

However, *S. coelicolor* and *S. avermitilis* are carrying an enormous pool of P450 enzymes, 20 cytochromes P450 and 30 cytochromes P450 respectively. Industrial applications could imply specific bacterial cytochromes P450's, which would activate the metabolic procedures in a way that that the modified enzymes could be employed for bioremediation, decontamination treatment, or biosynthesis of chemicals in a positive way [100]. From another point of view, knowledge of the cytochromes mechanisms involved in drug interactions is capital, not only in preventing drug toxicity or adverse effects, but also in drawing new more effective therapeutic schemes.

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