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LIVER AND METABOLISM

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ABSTRACT

Liver is the paramount organ for maintaining the body's internal environment. There is currently no way to indemnify for the absence of liver function. Its major influence is on the flow of foreign particles and controls the metabolism of drugs and nutrients. As most drugs are taken orally these are the important substances which are passed through liver for first pass metabolism, thereby converting into metabolites which are compatible with the human body. The present review is to provide an understanding on the drug metabolism by the liver. Classification of drugs based on their hepatic extraction and the working of cytochrome P450 enzymes is also elucidated. Certain substances induce or inhibit the metabolism of some drugs, which may lead to sub-therapeutic drug concentration and toxicity respectively. This review can be helpful to figure out the mechanism for diversification in drug metabolism.

Keywords: Liver, metabolism, induction, inhibition, drug biotransformation.

INTRODUCTION

The liver may be contemplated as the most vital organ in drug toxicity because it is functionally arbitrate between the site of absorption and the systemic circulation and is a major site of metabolism and elimination of foreign substances; these feature deliver it a preferred target for drug toxicity.[1] It is the largest internal organ weighing about 1.5 kg and is located in the right upper quadrant of the abdominal cavity, resting just below the diaphragm. It is reddish brown in color with four lobes of unequal size and shape.

The liver plays an astounding array of vital functions in the maintenance, performance and regulating homeostasis of the body. It is involved with most of the biochemical pathways to growth, fight against disease, nutrient supply, energy provision and reproduction.[2] The major functions of the liver are carbohydrate, protein and fat metabolism, detoxification, secretion of bile and storage of vitamin. Thus, to maintain a healthy liver is a compelling factor for the overall health and well being.[3]

As most drugs are taken orally the liver is the portal to the tissues for such compounds following absorption from the gastrointestinal tract. The liver is, therefore, a vulnerable organ, being exposed to both the parent drug carried from the G.I. tract via the portal vein and to any metabolites produced which then enter the systemic circulation via the hepatic vein.[4] Drugs are most often eliminated by biotransformation and /or excretion into the urine or bile. The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal tubules. Therefore, lipid-soluble agents must first be metabolized in the liver. The overall aim of hepatic drug metabolism is to produce a more water soluble compound to facilitate the excretion of the drug in body fluids such as urine and bile, the primary routes of drug excretion.[5]

PHASES OF DRUG METABOLISM

The metabolism takes place in two phases, they are:

Phase I: Phase I reactions function to convert lipophilic molecules into more polar molecules by hydrolysis, oxidation and/ or reduction reactions.

Phase II: This phase consists of conjugation reactions. Many Phase I metabolites are too lipophilic to be retained in the kidney tubules. A subsequent conjugation reaction with an endogenous substrate, such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid, results in polar, usually more water-soluble compounds that are most often therapeutically inactive.

Reversal of order of the phases: Not all drugs undergo Phase I and II reactions in that order. For example, isoniazid is first acetylated (a Phase II reaction) and then hydrolyzed to isonicotinic acid (a Phase I reaction).

FIRST PASS EFFECT

the first-pass effect (also known as first-pass metabolism or presystemic metabolism) is a phenomenon of drug metabolism whereby the concentration of a drug is greatly reduced

before it reaches the systemic circulation. This first pass through the liver thus greatly reduces the bioavailability of the drug. Certain drugs has no significant loss by first pass metabolism as in case of ciprofloxacin.[6] Alternative routes of administration like suppository, intravenous, intramuscular, inhalational aerosol, transdermal and sublingual avoid the first-pass effect because they allow drugs to be absorbed directly into the systemic circulation. The efficacy of dietary substances also depends on the liver. For ex: in vivo efficacy of polyphenols depends on its metabolic conversion in intestinal cells, liver, and other tissues.[8]

Hepatic extraction and intrinsic clearance: Hepatic extraction (E) is a useful term to measure how easily the liver can process, or metabolize, a given drug or toxin. The term 'hepatic extraction' effectively means the difference between the drug level in blood that enters the liver (100 per cent) and the amount that escapes intact and unmetabolized (that is, 100 per cent minus the metabolized fraction).[7]

Clinically, most drugs' hepatic extraction ratios will either be:

- High ($E > 0.7$), or
- Low ($E < 0.3$),
- With a few agents falling into the intermediate category (E is > 0.3, but < 0.7).

High extraction drugs: For high extraction drugs, the particular enzyme system that metabolizes this drug may be present in large amounts and drug processing is very rapid. This often happens if the drug is very similar in structure to an endogenous agent, which is normally processed in great quantity on a daily basis. In the case of a high extraction drug, the inbuilt or ' intrinsic ' ability of the liver to metabolize the drug means that the only limitation in the liver's ability to metabolize this type of drug is its rate of arrival, which is governed by blood flow.

During intensive exercise, human liver blood flow can fall temporarily by more than 70%, but during normal day-to-day living, blood flow through the liver does not normally vary that much. This means that a high extraction drug will be cleared at a fairly predictable rate. However, hepatic blood flow can be significantly reduced in old age and end - stage cirrhotic alcoholism. Patients with impaired cardiac output, either as a result of congestive heart failure or myocardial infarction, also experience marked reductions in liver blood flow. All these

circumstances have been shown to reduce the clearance of high extraction drugs clinically and should be borne in mind during drug dosage determination in these patients.

Low extraction drugs: On the opposite end of the scale (E < 0.3), low extraction drugs are cleared slowly, as the metabolizing enzymes have some difficulty in oxidizing them, perhaps due to stability in the structure, or the low capacity and activity of the metabolizing enzymes. The metabolizing enzymes may also be present only in very low levels. These drugs are considered to be low intrinsic clearance drugs, as the inbuilt ability of the liver to remove them is relatively poor. If a low extraction drug is not extensively bound to protein (less than 50 per cent bound) then how much drug is cleared is related directly to the intrinsic clearance of that drug. In the case of a low extraction, strongly protein bound drug, then the liver finds clearance even more difficult, as the affinity of drug for the protein is much greater than the liver's affinity for the drug. The anticonvulsants phenytoin and valproate are both highly protein bound (> 90 per cent) and low extraction drugs and so the amount of these drugs actually cleared by the liver really depends on how much unbound or free drug there is in the blood. Therefore, clearance is proportional to the ability of the liver to metabolize the drug ($Cl_{intrinsic}$) as well as the amount of unbound or free drug in the plasma that is actually available for metabolism. Hepatic blood flow changes have little or no effect on low extraction drug plasma levels, but if the intrinsic ability of the liver to clear a low extraction drug falls even further (due to enzyme inhibition or gradual organ failure), there will be a significant increase in plasma and tissue free drug levels and dosage adjustment will be necessary. Conversely, if the intrinsic clearance increases then free drug levels may fall and the therapeutic effects of the agent will be diminished.

Role of the liver: Drugs, toxins and all other chemicals can enter the body through a variety of routes. The major route is through the digestive system, but chemicals can by - pass the gut via the lungs and skin. Although the gut metabolizes many drugs, The majority of the reactions of drug metabolism are carried out in the liver.[9] CYPs and other metabolizing enzymes reside in the liver hepatocytes. These cells must perform two essential tasks at the same time. They must metabolize all substances absorbed by the gut whilst also processing all agents already present (from whatever source) in the peripheral circulation. This would not be possible through the conventional way that organs are usually supplied with blood from a single arterial route carrying oxygen and nutrients, leading to a capillary bed that becomes a venous outflow back to the heart and lungs. The circulation of the liver and the gut

have evolved anatomically to solve this problem by receiving a conventional arterial supply and a venous supply from the gut simultaneously; all the blood eventually leaves the organ through the hepatic vein towards the inferior vena cava.

The hepatic arterial blood originates from the aorta and the venous arrangement is known as the hepatic portal system, which subsequently miniaturizes inside the liver into sinusoids, which are tiny capillary blood - filled spaces. This capillary network effectively routes everything absorbed from the gut direct to the hepatocytes, which are bathed at the same time in oxygenated arterial blood. Metabolic products can leave the hepatocytes through the hepatic vein or by a separate system of canalicali , which ultimately form the bile duct, which leads to the gut. So, essentially, there are two blood routes into the hepatocytes and one out, which ensures that no matter how a xenobiotic enters the body, it will be presented to the hepatocytes for biotransformation.

CYTOCHROME P 450s

CYPs belong to a group of enzymes which all have similar core structures and modes of operation. They play a key role in more than 75 per cent of all drug biotransformations. In all living things, over 7,700 individual CYPs have been described so far, although humans make do with just 57; of these, only 15 metabolize drugs and other xenobiotics. Many of the other CYPs are poorly understood in terms of their physiological function and regulation and have been termed ‘orphan’ CYPs. To date, more than 780 CYP families have been found in nature in total, but only 18 have been identified in humans. The families are numbered, such as CYP1, CYP2, CYP3, etc. Subfamilies are identified as having 55 per cent sequence homology; these are identified by using a letter and there are often several subfamilies in each family such as CYP1A, CYP2A, CYP2B, CYP2C, etc. Regarding the individual CYP enzymes themselves, these ‘isoforms’ originate from alleles, or slightly different versions of the same gene. They are given numbers within the subfamily, such as CYP1A1 or CYP1A2 and these isoforms have 97 per cent of their general sequences in common.

Features of CYPs: CYPs exist in a lipid microenvironment with a haem group in their active site which contains iron, which is a crucial and highly conserved part of their structures. All CYPs contain at least one binding area in their active site, which is the main source of their variation and their ability to metabolize a particular group of chemicals. To catalyze substrate oxidations and reductions, CYPs exploit the ability of a metal, iron, to gain or lose electrons.

They all bind and activate oxygen as part of the process of metabolism and are capable of reduction reactions that do not require oxygen.

Functions of CYPs: CYP isoforms have evolved to:

• make a molecule less lipophilic (and often less stable) as rapidly as possible;

• make some molecules more vulnerable to conjugation.

The first step is the binding of the substrate. Individual CYPs bind groups of very broadly similar chemical structures. This is partly achieved by the size and physicochemical characteristics of the molecule. The processes involved in the orientation of substrates to proximity with the haem iron are complex, but once an agent is presented to the iron, oxidation and occasionally reduction, can then occur.

Role of oxidation: CYP metabolism is almost always some form of oxidation, which can achieve their main aims. Oxidizing a molecule can have three main effects on it, as follows.

- *Increase in hydrophilicity:* Forming a simple alcohol or phenol is often carried out to make a molecule soluble in water so it can be eliminated without the need for any further metabolic input.
- *Reduction in stability leading to structural rearrangement:* Some chemical structures are inherently less stable than others and any prototype drugs that are unstable and have the potential to react with cellular structures are weeded out in the drug discovery process. However, the process of CYP - mediated metabolism, where a stable drug is structurally changed, can form a much more reactive and potentially toxic product. There is a risk that the new molecule may be very reactive and dangerous indeed and may attack the CYP itself or the surrounding cellular structures. Although this does happen, evolution has retained the advantages of CYPs, such as their ability to process virtually any required molecule, through the appearance of conjugation and detoxification systems that contain and usually quench the reactivity of these agents. With CYP oxidation processes, the evolution of attendant detoxification systems ensures that the risk to the cell of creating a reactive species usually pays off and a molecule can be quite radically changed in terms of its physicochemical properties without problems. It can also pave the way for further metabolism, such as conjugation.
- *Facilitation for conjugation:* Many oxidative metabolites are much more vulnerable than their parent molecules to reaction with water - soluble groups such as glucuronic acid and

sulphates. Once a conjugate is formed, this vastly improves water solubility and Phase III transport systems will generally remove it from the cell and into the blood.[7]

THE ROLE OF METABOLISM IN THE SAFE AND EFFECTIVE USE OF DRUGS

The extent of metabolism can determine the efficacy and toxicity of a drug by controlling its biological half-life. Among the most serious considerations in the clinical use of drugs are adverse drug reactions. If a drug is metabolized too quickly, it rapidly loses its therapeutic efficacy. This can occur if specific enzymes involved in metabolism are overly active or are induced by dietary or environmental factors. If a drug is metabolized too slowly, the drug can accumulate in the bloodstream; as a consequence, the pharmacokinetic parameter AUC (area under the plasma concentration–time curve) is elevated and the plasma clearance of the drug is decreased. This increase in AUC can lead to over-stimulation of some target receptors or undesired binding to other receptors or cellular macromolecules. An increase in AUC often results when specific xenobiotic-metabolizing enzymes are inhibited, which can occur when an individual is taking a combination of different therapeutic agents and one of those drugs targets the enzyme involved in drug metabolism.[10]

Induction of Drug Metabolism

Xenobiotics can influence the extent of drug metabolism by activating transcription and inducing the expression of genes encoding drug-metabolizing enzymes. Thus, a foreign compound may induce its own metabolism, as may certain drugs.

One potential consequence of this is a decrease in plasma drug concentration over the course of treatment, resulting in loss of efficacy, as the auto-induced metabolism of the drug exceeds the rate at which new drug enters the body. A particular receptor, when activated by a ligand, can induce the transcription of a battery of target genes. Among these target genes are certain CYPs and drug transporters. Thus, any drug that is a ligand for a receptor that induces CYPs and transporters could lead to drug interactions.[10]

Inhibition of drug metabolism

When drug clearance is slowed or even stopped for any reason, the consequences are more dangerous and occur much more rapidly compared with enzyme induction. Generally, the intended pharmacological effects of the drugs will be greatly intensified, leading to a clear manifestation of symptoms in the patient. A drug may induce potentially serious unintended pharmacological effects that are only seen at high doses, considerably above the normal

range. These effects, sometimes known as 'off target' pharmacological actions, may or may not have been seen in the initial pre – clinical (animal) toxicity testing of the drug.

CYPs are enzymes like any other in the body and they are inhibited according to the same general principles as other enzymes. How tightly a chemical interacts with a CYP isoform is based on how powerful is the mutual attraction (affinity) between the chemical and the various areas of the active site of the enzyme. In the case of CYPs and any given enzyme, affinity must be strong enough to ensure the substrate is bound for sufficient time to process it to a product. The quicker this process occurs, the faster the 'turnover' of the enzyme and the more efficient it is. The enzyme cycles hundreds of times a second. If any single aspect of substrate binding or processing (oxidation or reduction), followed by product release is prevented, the sequential nature of these events means that the enzyme stops functioning. Broadly, inhibitors of CYPs may frustrate the enzymes ' operating processes in two main ways, with varying impact on drug clearance and the individual enzyme 'health' and survival. At high concentrations, many inhibitors might block several CYP subfamilies, but at lower concentrations, they show more selectivity and their potency in blocking individual isoforms can be measured. Inhibition itself can occur through four main processes: competitive, non-competitive, uncompetitive and mechanism-based. Which type of inhibition occurs with various drugs can depend on many factors, such as drug concentration and the characteristics of a particular CYP isoform. Many drugs can act as competitive inhibitors with one CYP and non - competitive with others. One potential consequence of inhibition is an increase in plasma drug concentration over the course of treatment, resulting in toxicity, as the auto-inhibition metabolism of the drug lowers the drug clearance from the body.Metabolism may also play a role in many disease, as an instance it is hypothesized that hyperglycemia leads to a decrease in epileptic seizure threshold by increasing metabolism of gamma-aminobutyric acid accordingly decreasing the level of GABA, so resulting in a reduction of seizures threshold.[11]

CONCLUSION

Liver plays an important role in metabolizing the foreign substances which enters into the body and passes through it. Liver is directly or indirectly associated with drug-drug interactions and adverse drug reactions, which are the frequent problems experienced in the present generation. There are plenty of factors which influence the functions of liver as discussed in the article.

CONFLICT OF INTEREST

Authors state that there is no conflict of interest.

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