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CYTOCHROME OXIDASE ENZYME- ITS ROLE IN DRUG METABOLISM- REVIEW

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ABSTRACT

Oxidation is probably the most common reaction in xenobiotic metabolism. This reaction is catalyzed by a group of membrane bound monooxygenases found in the smooth endoplasmic reticulum of the liver and other extra hepatic tissues, called the cytochrome P450 monooxygenase enzyme system.CYP450 functions as a multicomponent electron transport system responsible for the oxidative metabolism of variety of endogenous substrate such as the steroids, fatty acids, prostaglandins, and bile acids, exogenous substances including drugs, carcinogens, insecticides, plant toxins, environmental pollutants, and other foreign chemicals. The Enzyme systems carring out this biotransformation are referred to as mixed-function oxidase or monooxygenase. The versatility of Cytochrome P-450 in carrying out a variety of oxidation reaction on a multiple forms of the Enzyme. The reaction requires both molecular oxygen and the reducing agents NADPH. The Mixed function oxidase system is actually made up of several; components, the most important being the super family of Cytochrome P-450 enzymes. The Presence of this enzyme in many other tissues has drug- Oxidizing capability too.

KEY WORDS: CYP450, P450.

INTRODUCTIONS

The endoplasmic reticulum of mammalian cells plays an important role in drug metabolism. A variety of enzymes that carries out a large number of vital cellular functions and detoxification are located in the endoplasmic reticulum. This intracellular membrane is richly endowed with the mono-oxygenase system which catalyses various oxidation reduction reactions involved in drug metabolism. The most important functions of CYP450 is its ability to activate molecular oxygen, permitting the incorporation of one atom of oxygen into an organic substrate molecule concomitant with the reduction of the other atom of oxygen to water.[1] The introduction of a hydroxyl group into the hydrophobic substances molecule provides a site for subsequent conjugations with hydrophilic compounds, thereby increasing the aqueous solubility of the product for its transport and excretion for the organism. This enzyme system not only catalyzes xenobiotic transformation in way that usually lead to detoxication, but in some cases, in way that lead to products having greater cytotoxic, mutagenic, or carcinogenic properties. Conclusive evidence about the presence of cytochrome P450 and its role in drug metabolism was documented in 1962 due to efforts of G.R. Williams of Johnson foundation for medical physic, university of Pennsylvania. One important feature of the hepatic Cytochrome P-450 mixed function oxidize system is its ability to metabolize an almost unlimited number of diverse substrate by a variety of oxidative transformation.[7] This versatility is believed to be due to the substrate nonspecificity of Cytochrome P-450 as well as to the presence of multiple forms of the enzyme.[8] The Cytochrome P-450 monooxygenase are located in the endoplasmic reticulum, a highly organized and complex network of intracellular membranes that is particularly abundant in tissue such as the liver.[9]

CYTOCHROME P450 ENZYME NOMENCLATURE

Table No. 1

Cytochrome P450 Enzyme Nomenclature

Sr. No	Name
CYP- Arabic Number-Capital Letter- Arabic Number	
1	CYP: Cytochrome P-450 enzymes
2	Arabic Number: Family (CYP 1, CYP 2, CYP 3, etc)
Must have more than 40% identical amino acid sequence	
3	Capital letter: Subfamily (CYP 1A, CYP 2C, CYP 3A, etc)
Must have more than 55% identical amino acid sequence	

4	Arabic number: Individual enzyme in a subfamily (CYP 1A2, CYP 2C9, CYP 2D6, CYP 2E1, CYP 3A4, etc)

COMPONENTS OF CYP450

CYP450 consists of at least two protein components: a haem protein called cytochrome P450 and a flavoprotein called NADPH- CYP450 reeducates containing both flavin dinucleotides. Cytochrome P450 can be defined as any hemoprotein that has an ability to show a peak absorbance at 450 nm, when it is reeducated and react with carbon monoxide to form a complex.[2] Third components essential for electron transport form NADPH to CYP450 is a phospholipids, phosphatidylcholine that facilitates the transfer of electron from NADPH- CYP450 reeducates to CYP450. Of the three components involved in microsomal oxidative xenobiotic metabolism, CYP450 is important because of its vital role on oxygen activation and substrate binding. CYP450 is an integral membrane protein deeply imbedded in the membrane matrix. The term includes either a single molecular species or a group of cytochromes. At least 15 different cytochrome of P450 type have been identified. They differ in substrate selectivity, molecular weight, catalytic ability, immunological reactivity's, electrophoretic mobility or response to enzyme inducers. The enzyme inducer that cause an increase in the activity of microsomal enzyme include, Phenobarbital, steroidal hormones and 3,4-benzpyrene.

CYTOCHROME P450 ACTIVITY IN VARIOUS ORGANS

Cytochrome P450 hemoproteins are presents in relatively higher concentration in liver and adrenals. The location of cytochrome P450 is not restricted to microsomes of liver but they have been reported to be presents in microsomes of the kidney, intestinal mucosa, lungs, brain, Skin, testis and placenta. Spleen, gonads, eyes and leukocytes also exhibit less significant cytochrome P450 activity. Some higher plants along with yeasts, molds, and bacteria also have cytochrome P450 activity.[2]

Table No. 2: Cytochrome P450 relative activity.

Organ	Relative activity (%)
Liver	100
Lung	20-30
Kidney	09
Intestine	07
Placenta	05
Adrenal	02
Skin	01

The nonester types are primarily metabolized in the liver by CYP450.[3]

Mechanism action of Cytochrome P450

The mechanism by which these mixed function oxidizes operate may involve a series of steps, each step being controlled by an appropriate enzyme system. These steps can be either oxidative or reductive in nature. The catalytic role that the Cytochrome P-450 monooxygenase system play in the oxidation of xenobiotics is sum marized in the cycle in figure 1.

When the system is at rest the iron is in the fully oxidized Fe^{3+} state. It has been proposed that the substrate initially binds to the active site. This is followed by a reduction of the Fe^{3+} of the cytochrome P-450 to the Fe^{2+} state by a one electron transfer catalyzed by P-450 reductase. At this point molecular oxygen binds to the Fe^{2+} and is converted by a series of steps to an activated oxygen species. This species react to form the appropriate products.

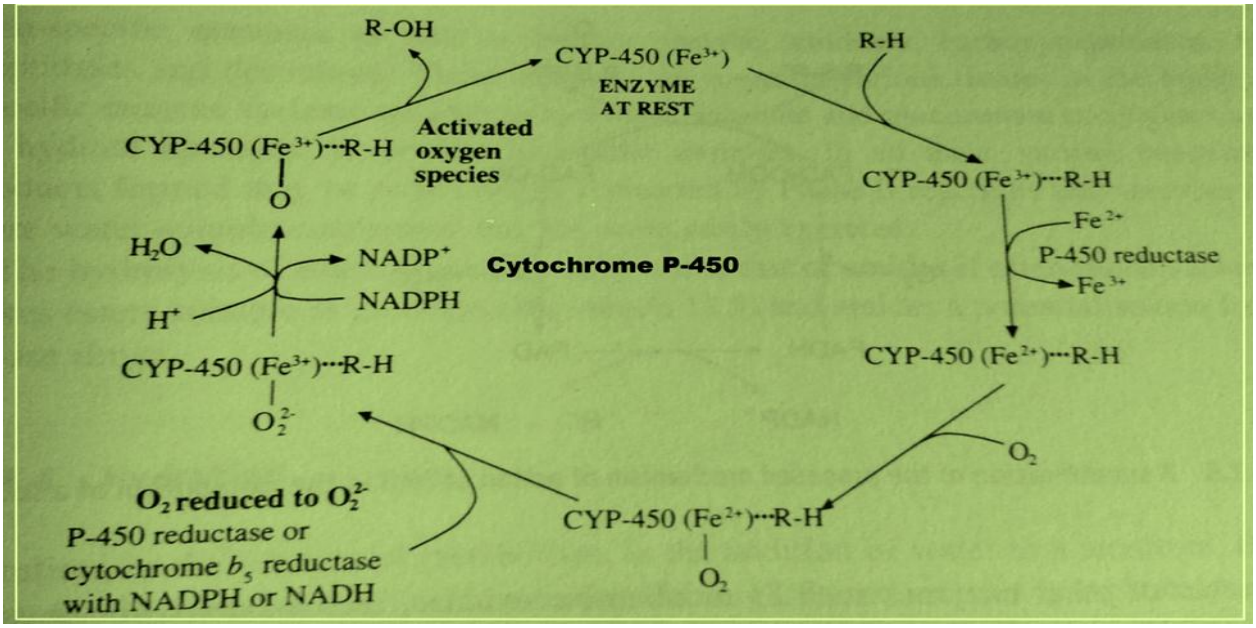

Fig-1: The proposed mechanism of action of Cytochrome P-450.

The completed system is non-specific, catalyzing the oxidation of a wide variety of substrate. This is probably due to both the non-selectivity of the enzymes and also the existence of numerous isozymes. Furthermore, liquid soluble xenobiotics are good substrate for the cytochrome p-450 monooxygenase because high concentration of the enzymes system is found in lipoidal tissue. Flavin monooxygenases are also an important family of non-selective mixed function oxidizes. These enzymes, which have a FAD prosthetic group, require either NADH or NADPH as coenzyme.[4]

CONCLUSION

Cytochrome oxidase enzyme is considered to be an important in pharmaceutical medicinal chemistry which is important role in drug metabolism. Thus we can say that this proposed work of the Cytochrome oxidase enzyme would be very useful.

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