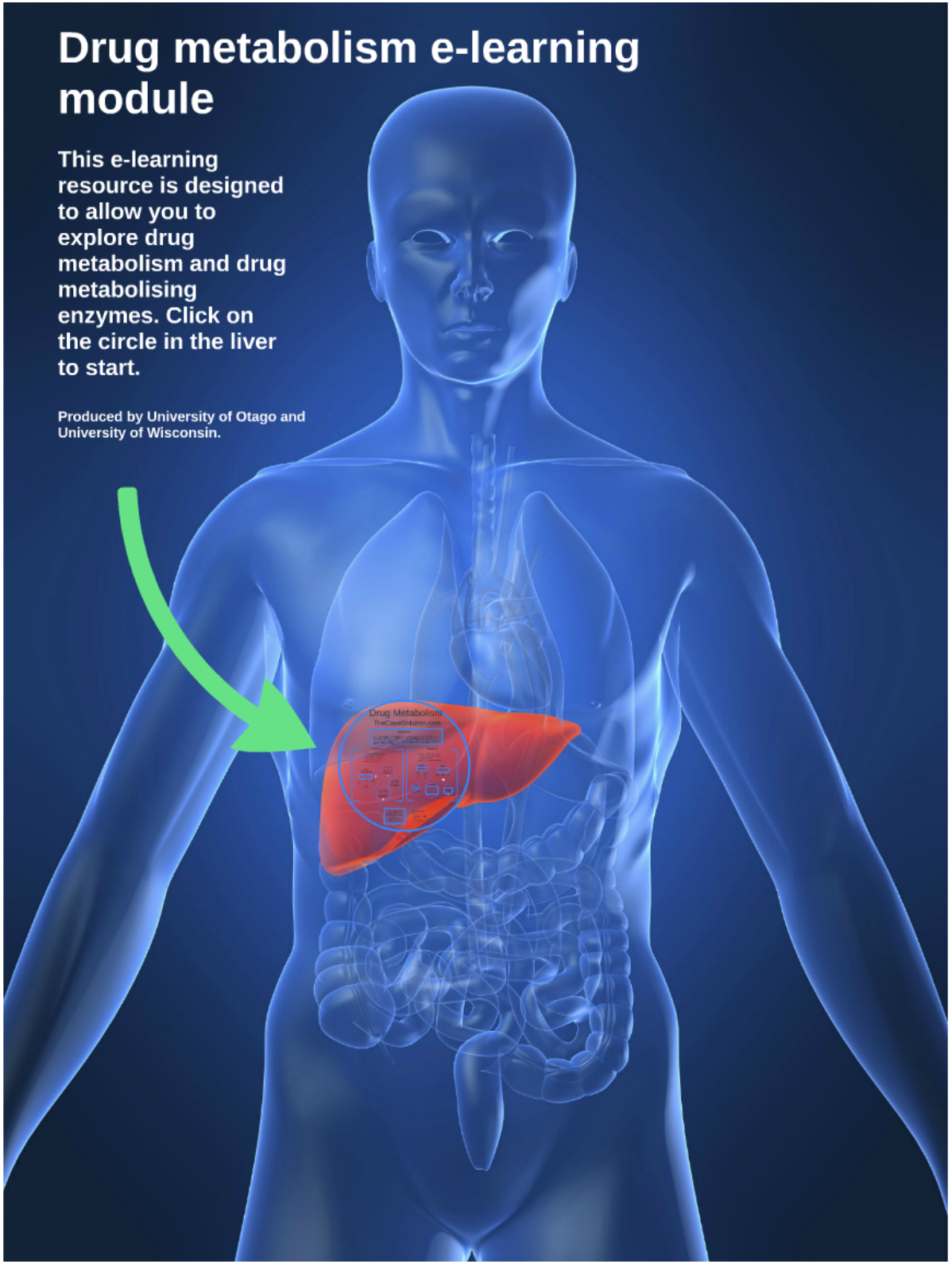
Drug metabolism e-learning module

This e-learning resource is designed to allow you to explore drug metabolism and drug metabolising enzymes. Click on the circle in the liver to start.

Produced by University of Otago and University of Wisconsin.



Drug Metabolism

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Overview

In 1947 R. T. Williams noted that enzyme-catalyzed biotransformation of drugs, dietary substances, and other synthetic and environmental agents, i.e., xenobiotics, can be by asynthetic and/orsynthetic reactions. Enzymes catalyzing asynthetic,or so-called Phase 1, reactions are thus classified broadly as all those catalyzing the oxidation, reduction, and hydrolysis of xenobiotics. Enzymes in this group include, but are not limited to, the mixed-function oxidases more commonly known as cytochrome P450 monooxygenases, monoamine and diamine oxidases, aldehyde dehydrogenases, aldehyde oxidase, alcoholde hydrogenases, quinone oxidoreductases, short-chain dehydrogenases/reductases, aldo-keto reductases, and esterases. Enzymes catalyzing synthetic, or so-called Phase 2, reactions are thus classified broadly as all those catalyzing the conjugation of xenobiotics to endogenous molecules, e.g., glucuronic acid, sulfate, glutathione, acetate, or a methyl group. Representative enzymes in this group include, but are not limited to, the UDP-glycosyltransferases, sulfotransferases, glutathione S-transferases, N-acetyltransferases, and methyltransferases

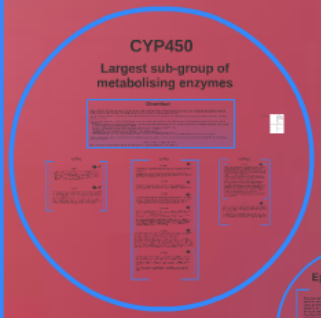
Phase 1

Introduce a functional group
- Increases water solubility
- Increases reactivity

Produce can be excreted or metabolised further.

CYP450

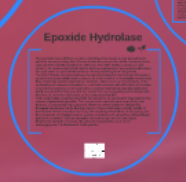
Largest sub-group of metabolising enzymes



Dehydrogenase

Esterases

Epoxide Hydrolase



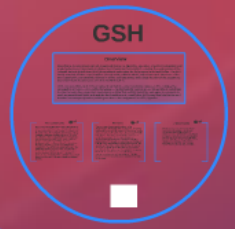
Phase 2

Conjugates a large group
- Increases water solubility
- Increases size

Product is normally excreted.

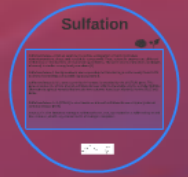
UDPGT

GSH



Acetylation

Sulfation



Methylation

Drug metabolising enzymes are found throughout the body but the highest concentrations are found in the liver.

These symbols indicate whether the enzyme is relevant to:

- Clinical drug metabolism

or

- Environmental chemical metabolism.

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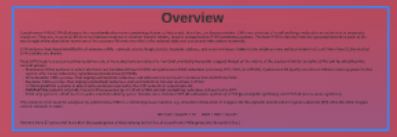

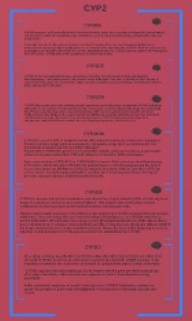

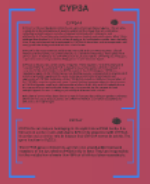

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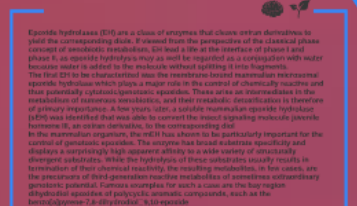

CYP450

Largest sub-group of metabolising enzymes

Overview

Cytochromes P450 (CYPs) belong to the superfamily of proteins containing a haem co-factor and, therefore, are haemoproteins. CYPs use a variety of small and large molecules as substrates in enzymatic reactions. They are, in general, the terminal oxidase enzymes in electron transfer chains, broadly categorised as P450-containing systems. The term P450 is derived from the spectrophotometric peak at the wavelength of the absorption maximum of the enzyme (450 nm) when it is in the reduced state and complexed with carbon monoxide.

CYP enzymes have been identified in all domains of life - animals, plants, fungi, protists, bacteria, archaea, and even in viruses. However, the enzymes have not been found in E. coli. More than 21,000 distinct CYP proteins are known.

Most CYPs require a protein partner to deliver one or more electrons to reduce the iron (and eventually molecular oxygen). Based on the nature of the electron transfer proteins, CYPs can be classified into several groups:

- Microsomal P450 systems in which electrons are transferred from NADPH via cytochrome P450 reductase (variously CPR, POR, or CYPOR). Cytochrome b5 (cyb5) can also contribute reducing power to this system after being reduced by cytochrome b5 reductase (CYB5R).
- Mitochondrial P450 systems, that employ adrenodoxin reductase and adrenodoxin to transfer electrons from NADPH to P450.
- Bacterial P450 systems, that employ a ferredoxin reductase and a ferredoxin to transfer electrons to P450.
- CYB5R/cyb5/P450 systems in which both electrons required by the CYP come from cytochrome b5.
- FMN/Fd/P450 systems originally found in Rhodococcus sp. in which a FMN-domain-containing reductase is fused to the CYP.
- P450 only systems, which do not require external reducing power. Notable ones include CYP5 (thromboxane synthase), CYP8 (prostacyclin synthase), and CYP74A (allene oxide synthase).

The most common reaction catalysed by cytochromes P450 is a monooxygenase reaction, e.g., insertion of one atom of oxygen into the aliphatic position of an organic substrate (RH) while the other oxygen atom is reduced to water:

$$RH + O_2 + NADPH + H^+ \rightarrow ROH + H_2O + NADP^+$$

Humans have 57 genes and more than 59 pseudogenes divided among 18 families of cytochrome P450 genes and 43 subfamilies.[

CYP1

CYP1A1

CYP1A2

CYP2

CYP2B6

CYP2C8

CYP2C9

CYP2C19

CYP2D6

CYP2E1

CYP3A

CYP3A4

CYP3A7

Epoxide Hy

Epoxide hydrolases (EH) are a class of enzymes t
yield the corresponding diols. If viewed from the p
concept of xenobiotic metabolism, EH lead a life a
phase II, as epoxide hydrolysis may as well be reg
because water is added to the molecule without s
The first EH to be characterized was the membran

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CYP2

CYP2B6

CYP2B6 enzymes synthesise cholesterol, steroids and other lipids. Its expression is induced by phenobarbital. The enzyme is known to metabolize some xenobiotics, such as the anti-cancer drugs cyclophosphamide and ifosphamide.

Transcript variants for this gene have been described; however, it has not been resolved whether these transcripts are in fact produced by this gene or by a closely related pseudogene, CYP2B7. Both the gene and the pseudogene are located in the middle of a CYP2A pseudogene found in a large cluster of cytochrome P450 genes from the CYP2A, CYP2B and CYP2F subfamilies on chromosome 19q.

xylase). It is involved in the
ic aromatic hydrocarbons,
g it to an epoxide. In this
y CYP1A1 to form BP-7,8-
blase (EH) to form BP-7,8-
to form BP-7,8-
en.

CYP3A4 is induced by gluc
is involved in the metabolis
including acetaminophen, c
erythromycin. The enzyme
undergo deactivation by CY
Also, many substances are
many protoxins being toxic

CYP3A4 is the most commo
members of this family, it is
an iron atom. In humans, th
is part of a cluster of cytoch

Table of CYP450 isoforms

Family	Function	Members	Names
CYP1	drug and steroid (especially estrogen) metabolism, benzo(a)pyrene toxification	3 subfamilies, 3 genes, 1 pseudogene	CYP1A1, CYP1A2, CYP1B1
CYP2	drug and steroid metabolism	13 subfamilies, 16 genes, 16 pseudogenes	CYP2A6, CYP2A7, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2F1, CYP2J2, CYP2R1, CYP2S1, CYP2U1, CYP2W1
CYP3	drug and steroid (including testosterone) metabolism	1 subfamily, 4 genes, 2 pseudogenes	CYP3A4, CYP3A5, CYP3A7, CYP3A43
CYP4	arachidonic acid or fatty acid metabolism	6 subfamilies, 12 genes, 10 pseudogenes	CYP4A11, CYP4A22, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4F22, CYP4V2, CYP4X1, CYP4Z1
CYP5	thromboxane A2 synthase	1 subfamily, 1 gene	CYP5A1
CYP7	bile acid biosynthesis 7-alpha hydroxylase of steroid nucleus	2 subfamilies, 2 genes	CYP7A1, CYP7B1
CYP8	varied	2 subfamilies, 2 genes	CYP8A1 (prostacyclin synthase), CYP8B1 (bile acid biosynthesis)
CYP11	steroid biosynthesis	2 subfamilies, 3 genes	CYP11A1, CYP11B1, CYP11B2
CYP17	steroid biosynthesis, 17-alpha hydroxylase	1 subfamily, 1 gene	CYP17A1
CYP19	steroid biosynthesis: aromatase synthesizes estrogen	1 subfamily, 1 gene	CYP19A1
CYP20	unknown function	1 subfamily, 1 gene	CYP20A1
CYP21	steroid biosynthesis	2 subfamilies, 1 gene, 1 pseudogene	CYP21A2
CYP24	vitamin D degradation	1 subfamily, 1 gene	CYP24A1
CYP26	retinoic acid hydroxylase	3 subfamilies, 3 genes	CYP26A1, CYP26B1, CYP26C1
CYP27	varied	3 subfamilies, 3 genes	CYP27A1 (bile acid biosynthesis), CYP27B1 (vitamin D3 1-alpha hydroxylase, activates vitamin D3), CYP27C1 (unknown function)
CYP39	7-alpha hydroxylation of 24-hydroxycholesterol	1 subfamily, 1 gene	CYP39A1
CYP46	cholesterol 24-hydroxylase	1 subfamily, 1 gene	CYP46A1
CYP51	cholesterol biosynthesis	1 subfamily, 1 gene, 3 pseudogenes	CYP51A1 (lanosterol 14-alpha demethylase)