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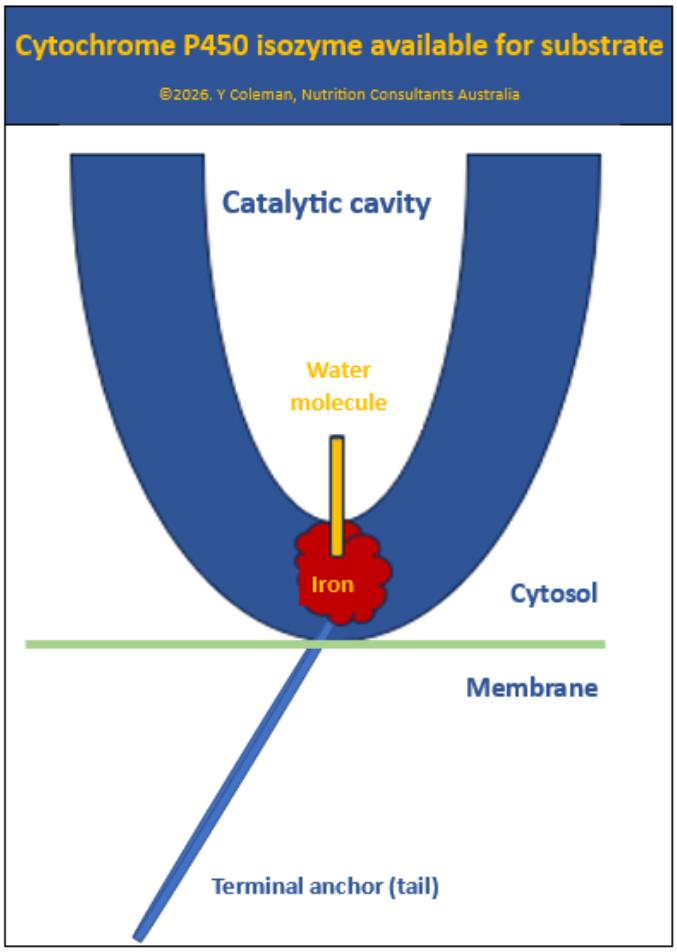


About Cytochrome P450 Isozymes

Y Coleman

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Cytochrome P450 isozymes are important in many nutrition and xenobiotic metabolic processes. They primarily convert endogenous (from within body) and exogenous (from outside body) lipid-soluble compounds into easily-excreted water-soluble metabolites.

Regulatory processes require interactions with defined CYP P450s isozymes to be evaluated in the drug discovery process. The FDA-defined list of cytochromes includes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 + CYP2E1.

Cytochromes are referred to interchangeably as enzymes, isoenzymes, or isozymes. Isozymes are enzymes with either different amino acid sequences, or different genes, that catalyze the same biochemical reactions.

This post is a general overview of cytochrome P450 isozymes and their global functions and mechanisms of action.

Cytochrome P450 Isozymes (CYP P450s)

CYP P450 isozymes are haemoproteins ie iron-containing, that are also known as monooxygenases, or mixed-function oxidases.

Locations

These isozymes are distributed throughout the body, and primarily located in the small intestine, liver, and kidneys.

Within cells, CYP P450s are typically located in the –

- endoplasmic reticulum membrane. These isozymes primarily catalyze exogenous compounds such as drugs.

- inner mitochondrial membrane. These isozymes primarily catalyze endogenous metabolic compounds such as cholesterol.

Functions

Processes in which they are essential include -

- **Metabolic.** Includes caffeine, cofactors, unsaturated fatty acids, xenobiotics, including drugs, fat-soluble vitamins, Vitamin D, retinoids.
- **Regulatory**. Includes fatty acids.
- **Bioynthesis.** Includes steroids, hormones, eicosanoids, cholesterol, bile acid.

Their activity can be altered by factors including diet, nutrients, gut microbiota, age, gender, genetic polymorphisms, xenobiotics, disease and allostery. Allostery is induced structural change that alters functionality.

Electron donors

The CYP P450 metabolic process requires the addition of 2 electrons in a 2-step process.

NADPH-cytochrome P450 reductase (CPR). Essential for the transfer of the first electron in the 2-step process.

Cytochrome-b5 reductase (CYB5R). A flavoprotein that typically transfers the second electron in the 2-step process.

Cytochrome b5 is the preferred second electron donor for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, CYP2E1. CYP2D6 interaction with Cytochrome b5 is weak.

Mechanisms of Action

The cytochrome P450 isozymes can be substrates, inhibitors, or inducers.

1. Substrates

Substrates are typically compounds metabolized by the isozyme. After the substrate is metabolized, the isozyme is available for the next substrate.

Example. Caffeine is a CYP1A2 substrate.

Cytochrome P450 + substrate metabolic sequence © 2026. Y Coleman, Nutrition Consultants Australia
Substrate enters the catalytic site to form a **CYP + substrate complex** plus a water molecule which it then displaces. This process changes the iron's spin state such that it will accept an electron.
CYP + substrate complex + ***NADPH-cytochrome P450 reductase-donated electron*** form an *iron + oxygen complex*.
Then either NADPH-cytochrome P450 reductase or cytochrome b5 donates an electron to the *iron + oxygen complex* to form Compound 1 + water. This water is expelled whilst Compound 1 is still within the **CYP + substrate complex**.
Compound 1 + **CYP + substrate complex** combine to form a water-soluble metabolite.
The water-soluble metabolite disassociates from the cytochrome catalytic site into the cellular environment.
Cytochrome is available for the next substrate.

2. Inhibitors

Inhibitors are typically compounds that stop the isozymes from functioning.

- Reversible inhibition means the isozyme is not destroyed in the metabolic process,

- irreversible inhibition (mechanism-based) means the isozyme is destroyed and must be resynthesized.

Slowing or inhibiting metabolism increases the risk of accumulation, toxicity, and adverse effects. It also activates prodrugs.

Inhibition can be within minutes, hours or days, and recovery can be within hours or days.

Example. Grapefruit juice inhibits CYP3A4 function (irreversible).

3. Inducers

Inducers are compounds that increase the actual number of isozymes and therefore indirectly increase the isozyme's rate of metabolism. They do not directly increase the isozyme's rate of metabolism.

Induction and recovery can be within hours or days.

Example. Ethanol is a CYP2E1 inducer.

Cytochromes in the absorption-metabolism process

Digestion is the progressive breakdown of orally-consumed items to their basic components. These components are typically either hydrophilic (water attracting), hydrophobic (water-repelling), lipophilic (fat attracting), lipophobic (fat repelling).

Lipophilic substances typically bind to micelles for transport to enterocytes in the intestinal brush border. (Micelles are structures that expedite the transport of poorly water-soluble agents). Membrane transporters then collect and transfer the lipophiles ((fat-based)) into cells where they locate their relevant cytochrome P450 isozymes. After metabolism they are ejected from the cell, typically for excretion.

Apart from some CYP3A4 exceptions, hydrophilic substances are not metabolized by cytochrome P450 isozymes. CYP3A4 can metabolize some hydrophilic compounds that are diverse in size and chemical structure.

Conclusions

Cytochrome P450 isozymes are essential in metabolic, regulatory, and biosynthesis processes by essentially optimizing excretion of fat-soluble compounds.

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