MedNut Mail

The How, What, Which, Where, When and Why of pharmaconutrition

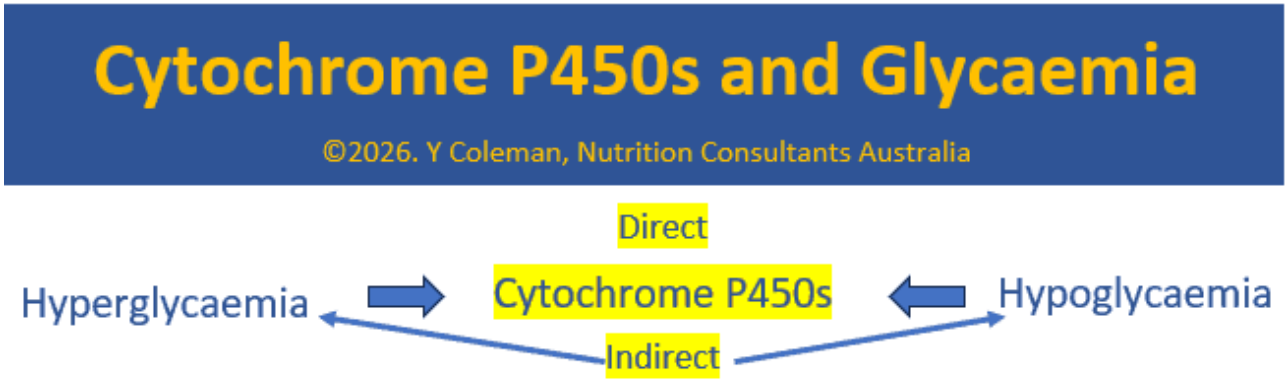


Cytochrome P450s and Glycaemia

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https://medicationsandnutrition.com/mednut-mail/



Cytochrome P450s are important in Phase 1 drug metabolism as they modify compounds to include a more water-soluble component. This modification enables either their excretion or Phase II metabolism.

The focus of this post is on the interactions between cytochrome P450s and glycaemic status.

Rather than referring to “xenobiotics, including prescribed medications”, I shall use “prescribed medications” or “drugs” interchangeably as a global alternative.

How Cytochrome P450s Alter Glycaemia

In physiological systems, including cytochrome P450 metabolic pathway, the interactions can be either direct or indirect -

Direct interactions: Cytochrome P450 isozymes do not directly participate in glucose metabolism.

Indirect interactions: Evidence is steadily increasing that cytochrome P450s can alter glycaemic status by altering drug availability.

Example 1 - inhibition: Glibenclamide is a CYP2C9 substrate; its unchanged form is the active form. If an inhibitor is prescribed then glibenclamide’s effectiveness is increased thus increasing the risk of hypoglycaemia.

Example 2 - induction: Causes increased rate of metabolism of the substrate drug which ultimately results in decreased therapeutic effect.

How Hyperglycaemia Alters Cytochrome 450s

Hyperglycaemia alters cytochrome P450s expression and activity indirectly via a variety of mechanisms, some of which are briefly outlined.

Cytokines

Chronic hyperglycaemia enhances the sustained activation and production of pro-inflammatory cytokines such as IL-6 and TNF-α. CYP1A2, CYP2C9, and CYP3A4 are downregulated by chronic low-grade inflammation.

Epigenetics

Hyperglycaemia induces epigenetic changes that form metabolic memory. Metabolic memory means that even after glycaemic status normalizes, the gene expression profile of metabolizing isozymes remains altered ie cannot be reversed. Consequently, altered drug metabolism and the risk of adverse drug reactions continue despite improved glycaemia.

Albumin Availability

Albumin is the body's primary carrier of substances including drugs, in the blood. Ultimately, reduced albumin availability means -

- reduced levels of drugs are available for cytochrome P450s metabolism and therefore their effectiveness is limited,

- the unmetabolized component of drugs increases the risks of adverse reactions.

Increased Urinary Albumin Excretion (UAE)

Hyperglycaemia is the primary trigger for renal endothelial dysfunction. Increased UAE is a marker of renal endothelial dysfunction in early-stage Type 2 Diabetes.

Glycated Albumin

Glycation is the binding of a sugar to a protein such as albumin, during hyperglycemia. Albumin availability is reduced and consequently so is the number drugs that can be carried. Hyperglycaemia increases the rate and extent of albumin glycation.

MedNut Mail post. 2025. Albumin and Glucose. *https://medicationsandnutrition.com/albumin-and-glucose/*

The Zinc Switch

Albumin production is dependent upon insulin's regulation of albumin's gene expression. Insulin activation is dependent upon albumin accepting its cleaved zincs (from released insulin hexamers).

MedNut Mail post. 2025. The Zinc Switch. *https://medicationsandnutrition.com/the-zinc-switch/*

Type 2 Diabetes

The impacts of Type 2 Diabetes on the activity levels of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 can be -

Decreased: CYP2C19 (46%), CYP2B6 (45%), CYP3A (38%), CYP2C9.

Unchanged: CYP2D6, CYP2E1.

Equivocal: CYP1A2. Activity can be dependent on glycemic levels and may be induced by poor glycemic control.

How Hypoglycaemia Alters Cytochrome 450s

Cytokines

Cytokine production depends mainly on blood glucose levels. Hypoglycaemia downregulates cytokine production likely in a glucose concentration-dependent manner.

Fasting

Short-term fasting influences CYP1A2, CYP2C9 and CYP2D6 drug metabolism by altering systemic clearance. The fasting effect is cytochrome P450 isozyme-specific.

Other Mechanisms

NADPH (Nicotinamide Adenine Dinucleotide Phosphate)

NADPH is the activated form of niacin. It is important in both cytochrome P450 function and insulin release from pancreatic beta-cells.

Insulin resistance means cells are unable to, or have limited capacity to process glucose through NADPH-generating pathways. Consequently, NADPH availability is reduced, which means cytochrome P450s-mediated phase I metabolism is either reduced or stopped.

Insulin resistance

Peripheral insulin resistance causes beta-cells in the pancreas to increase insulin production. Chronic overproduction of insulin causes the generation of reactive oxygen species in the beta-cells which then causes endoplasmic reticulum stress. Sustained endoplasmic reticulum stress ultimately results in cytochrome P450s dysfunction and cell death.

How to Integrate Cytochrome P450s into Clinical Assessments

We need to know ALL the substrates, inhibitors and inducers being consumed ie prescribed medications, nutrients, foodstuffs, and food components.

This table identifies the Oral Hypoglycaemic Agents that are metabolized by cytochrome P450s. It also includes both their specific cytochrome isozyme(s), and their function ie whether they are metabolized (substrates), inhibited or induced.

Some Diabetes Drugs and Their Cytochrome P450 Isozymes

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Cytochrome P450	2C9			3A4			2C8		
Drug	Sub	Inh	Ind	Sub	Inh	Ind	Sub	Inh	Ind
Bromocriptine				Y	Y				
Glibenclamide	Y								
Glimepiride	Y								
Glyburide	Y			Y					
Linagliptin					Y				
Pioglitazone						Y	Y		
Saxagliptin				Y					

We then need to -

- identify the other prescribed drugs that inhibit or induce these OHA drugs,

- ascertain whether they are contributing to altered glycaemic status.

This information may also modify some of the “dietary non-compliant” blame-labelling that is ascribed to those with sustained poorly-controlled glycaemic status. Hopefully this information will acknowledge an iatrogenic (healthcare-induced) component is contributing to this chronic poor glycaemic control.

Useful Resources

Flockhart Table: This useful resource identifies whether a drug is a substrate, inhibitor, or inducer of cytochrome P450s. Sadly, it has not been updated since 2021.

Drug Interactions Flockhart Table. https://drug-interactions.medicine.iu.edu/main-table

Systems Biology: This paper summarizes relevant systems succinctly.

Interactions Between Hyperglycaemia, Drug Metabolism, and Toxicity Profiles: A Systems Biology Review. 2026. https://doi.org/10.59298/NIJSES/2026/71.713

Clinical Concerns

Chronic altered glycaemia means altered cytochrome P450s metabolism and therefore altered availability of prescribed medications. How do we manage -

- those whom we know have chronic hyperglycaemia such as those prescribed prednisolone?

- rebellious teenagers?

- those who fast either episodically (eg for clinical tests or interventions), or regularly (eg philosophical practice)?

Clinical Questions

Will you include the impacts of cytochrome P450 on glycaemic control as a standard component in your clinical assessments?

Conclusions

Cytochrome P450s inclusion in clinical assessments adds an extra layer of complexity, and potential benefit, to clinical assessments.

Cite

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Professional Notice

The information in this article is designed to support healthcare professionals. It is not an exhaustive clinical protocol. Healthcare professionals are advised to maintain adequate professional supervision to ensure Duty of Care obligations with respect to safe administration of medicines is met for each individual consumer.

Core Philosophy

Whilst medications have profoundly improved global health outcomes, they typically also introduce nutritional challenges. By proactively identifying and addressing these nutritional harms, we can bridge the gap towards achieving better health outcomes.

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