Dietary Supplement Use in the Elderly
National Institutes of Health

Polypharmacy & OTCs: Impact of Dietary Supplements on Gene Networks that Regulate Drug Clearance

Barry M. Forman, MD, PhD
Associate Professor
Beckman Research Institute
City of Hope National Medical Center
Duarte, California
Nuclear Hormone Receptors
Coactivator Recruitment

Activated Transcription
Orphan Nuclear Receptors
A New Endocrinology

Novel Ligands?
- Steroid
- Thyroid
- Retinoid
- Vitamin D
Hormonal Ligands

Classical Receptors
- Steroids
- Thyroid
- Retinoids
- Vitamin D

Orphan Receptors
- Metabolites
  - Lipids
  - Fatty acids
  - Sterols
  - Bile Acids
  - Xenobiotics
**SXR / PXR**

A steroid & xenobiotic receptor

- **Expression:** Liver & Intestine
- **Target Genes:** Cyp3A4
- **Ligands:** Phenobarbital, Rifampicin, Clotrimazole
- **Function:** Protection from Xenotoxins, Enhancement of Drug Metabolism, Mediator of Drug-Drug Interactions
  - Cyclosporin, HIV Protease Inhibitors, Birth Control “Pill”
Taxol
Chemotherapeutic agent

Efficacy: Breast & Ovarian Cancers
Activity: Microtubule Stabilization
Metabolism: Cyp3A4 & Cyp2C8
Taxol is a Specific Activator of hPXR

PXR vs other receptors
PXR & Taxol Degradation
Cyp3A4 & Cyp2C8

Primary Human Hepatocytes

- Rifampin
  Taxol

Cyp 3A4
Cyp 2C8
GAPDH
hPXR Expression
Liver & Intestine

Adapted from Blumberg et al., Lehmann et al., & Bertilsson et al.
PXR Function in the Intestine?

Regulation of MDR1

Human Intestinal Cells
LS180
PXR
A master regulator of drug clearance
Taxol & Taxotere

Related chemotherapeutic agents

Efficacy: Breast & Ovarian Cancers
Activity: Microtubule Stabilization

Taxol

Taxotere
**Taxol vs Taxotere**

Taxotere does NOT activate hPXR

![Graph showing comparison between Taxol and Taxotere](image-url)

- **X-axis:** Taxane (nM)
- **Y-axis:** Fold Activation
- **Legend:**
  - Taxol (solid line)
  - Taxotere (dotted line)
**Taxol vs Taxotere**

**Taxotere does NOT induce drug clearance**

![Graph showing comparison between Taxol and Taxotere](image)

**Metabolism**

- **Hepatocytes**
  - Taxol: 125
  - Taxotere: 300

**Efflux**

- **Intestine**
  - Taxol Efflux Rate: 2
  - Taxotere Efflux Rate: 3
Ritonavir is a PXR ligand

**Transfection**
- hPXR

**Ligand Binding**
- hPXR
- [3H]-SR12813

**Structure**
- Ritonavir
Steroid & Xenobiotic Receptor (PXR/SXR)

PXR ligands are Cyp3A4 substrates

Expression: Liver & Intestine

Function: Master regulator of drug & xenobiotic clearance

Target Genes:
- MDR1, MRP2, OATP2
- Cyp3A4, Cyp2C8, Cyp2B
- GSTa1, UGT1A, CAR
- Aminolevulinate synthase (ALAS), Por

Ligands:
- Common Drugs & Xenobiotics
- Endogenous Ligands?
- Dietary Supplements?
Triol: a Potent PXR Agonist

Cyp3A4 & PXR utilize common sterol substrates

5β-cholestan-3α,7α,12α-Triol

Cyp3A4

5β-cholestan-3α,7α,12α,25-Tetrol

Transfection Assay

Mouse PXR

EC₅₀: 3 μM
Cyp27 KO: Triol Accumulation & PXR Activation

Triol Accumulation

Cholic Acid

Hepatic Target Genes

Cyp27: +/+ -/-

Cyp3A11

Cyp2C

OATP2

GAPDH

Tribromoethanol Sleep Time
Species-specific responses

**Human PXR**

- Rifampicin: Fold Activation = 29
- PCN: Fold Activation = 1

**Mouse PXR**

- Rifampicin: Fold Activation = 33
- PCN: Fold Activation = 5
Widespread Use of Dietary Supplements

"Something from the supplement cart?"

© Cartoonbank.com
Widespread Use of Dietary Supplements
Future Research Needs & Resources
Predict and prevent herbal-drug interactions

- **Require comprehensive study of herbal meds for effects on:**
  - PXR activation
  - Endogenous PXR ligands
  - Expression of genes involved in drug clearance
  - Activity of P450 enzymes and transporters
  - Drug clearance in humanized mice
  - Human trials using non-invasive measures of drug clearance
  - Similar studies on related receptor CAR

- **Teach clinicians & patients**
  - Natural product ≠ Safety
  - Medical histories should document use of drug supplements
  - Create online database
  - Modify supplement use is counterindicated
  - FDA-like regulation? Standardize potency, efficacy, safety?

- **Explanation of interindividual differences in drug clearance?**
  - Polymorphisms in PXR
  - Polymorphisms in CAR