Herb-Drug Interactions Caused by the Nuclear Receptor PXR

Steven Kliewer
University of Texas Southwestern Medical Center
Dallas, TX
St. John’s Wort Causes Drug Interactions

PXR screens can be used to prevent herb-drug interactions

Phase I (oxygenases)
Phase II (conjugases)
Transporters
Nuclear Receptor Superfamily

48 NRs in human genome

Classical Receptors (12)
- Glucocorticoid
- Mineralocorticoid
- Progesterone
- Estrogen (α,β)
- Androgen
- Thyroid Hormone (α,β)
- Vitamin D
- all-trans Retinoic Acid (α,β,γ)

Orphan Receptors (36)
- CAR
- COUP (α,β,γ)
- DAX
- ERR (α,β,γ)
- FXR
- PXR
- PPAR (α,γ,δ)
- revErb (α,β)
- RXR (α,β,γ)
- ROR (α,β,γ)
- SF1 (α,β)
- SHP
- Tlx
- TR2 (α,β)
- NGFI-B (α,β,γ)
- PNR
Xenoprotection

Xenobiotics = foreign chemicals

- Inhaled
- Ingested
- Absorbed

Liver
Intestine

P450 enzymes
oxygenases
conjugation enzymes
transporters
**CYP3A Induction**

Expressed in liver and intestine
- Activated by xenobiotics
- Bind to XREs

**xenobiotics**
- rifampicin
- dexamethasone
- RU486
- clotrimazole
- troglitazone
- tamoxifen

**CYP3A**
- Protects against xenobiotics
- Causes drug-drug interactions

xenobiotics → CYP3A → HO-xenobiotics
**Pregnane X Receptor (PXR)**

- **human PXR**
  - DNA: 82%
  - Ligand: 94%

- **rabbit PXR**
  - DNA: 77%
  - Ligand: 96%

- **mouse PXR**
  - DNA: 76%
  - Ligand: 96%

- **rat PXR**
  - DNA: 76%
  - Ligand: 96%

- Cloned due to homology with other nuclear receptors
- Named on basis of activation by natural and synthetic C21 steroids (pregnanes), including pregnenolone 16\(\alpha\)-carbonitrile (PCN)
PXR Expression in Human

Northern blot

heart brain placenta lung liver muscle kidney pancreas spleen thymus prostate testis ovary small intestine colon PBL

[Image of a gel with bands at positions 9.5, 7.5, 4.4, 2.4, and 1.4]
CYP3A Inducers Activate
*Human, Rabbit, and Rat* PXR

Cell-based reporter assay

- rifampicin
- PCN
- dexamethasone
- RU486
- clotrimazole
- troglitazone
- tamoxifen

Reporter activity (fold)
PXR Regulates CYP3A

- Expressed in liver and intestine
- Activated by xenobiotics
- Binds to XREs

PXR

RXR

XRE

CYP3A

xenobiotics (e.g., drugs)

HO-xenobiotics

Other genes?
PXR Regulates Xenobiotic Metabolism

Liver RNA from mice treated with
- vehicle
- PCN

• Phase I (oxidation) enzymes
  - Cyp3a11 (3.5x)
  - Cyp2b10 (12x)
  - Aldh1a1 (2.1x)
  - Aldh1a7 (1.6x)

• Phase II (conjugation) enzymes
  - Ugt1a1 (2.8x)
  - Gst-a1 (16x)

• Transporters
  - Mdr1a (3.2x)
  - Mrp3 (3.0x)
  - Oatp2 (9.2x)
PXR Protects the Body from Toxins, *But…*

- **PXR Protects the Body from Toxins**
  - Causes Drug-Drug Interactions

- **xenobiotics**
  - rifampicin
  - dexamethasone
  - RU486
  - clotrimazole
  - troglitazone
  - tamoxifen
  - others?

- **Phase I Transporters**

- **Phase II Transporters**

- **>50% of drugs**
  - oral contraceptives
  - cyclosporin
  - warfarin
  - indinavir
  - nevirapine
  - irinotecan

- **xenobiotic metabolism**
St. John’s Wort

- Medicinal herb
- Widely used for depression
  - European sales of $6 billion (1998)
- Complex mixture of > two dozen chemicals
- Drug interactions
  - oral contraceptives
  - cyclosporin
  - warfarin
  - indinavir
  - nevirapine
  - irinotecan
St. John’s Wort Activates PXR

Cell-based reporter assay

EC₅₀ ~ 30 nM
SJW Interacts with Drugs

SJW is predicted to interact with most drugs

oral contraceptives
cyclosporin
warfarin
indinavir
nevirapine
irinotecan

Phase I
Phase II
Transporters

drug metabolism
SJW Interacts with Drugs

cyclosporin..............immunosuppressant
 tacrolimus..............immunosuppressant
 quazepam................sedative
 warfarin..................anticoagulant
 verapamil..............antihypertensive
 nifedipine.............antihypertensive
 omeprazole...........antiulcerative
 theophylline...........bronchodilator
 ethinylestradiol.......oral contraceptive

midazolam.......anesthetic
 nevirapine.......antiviral
 indinavir............antiviral
 irinotecan........antineoplastic
 gleevec............antineoplastic
 amitriptyline....antidepressant
 simvastatin.......anticholesterolemic
 digoxin............cardiotonic
 methadone.........analgesic
 alprazolam...........anxiolytic

Do other herbs activate PXR?
Gugulipid Activates PXR

- Derived from mukul myrrh tree
- Promoted for reducing cholesterol and treating obesity
- Accelerates the metabolism of two antihypertension drugs
  - diltiazem
  - propranolol

Gugulipid may counteract other drugs including statins
Hops Activates PXR

- Promoted for treating
  - insomnia
  - anxiety
  - indigestion
- Increases drug metabolizing enzymes in rodents

Hops is predicted to interact with most drugs
Herbs Activate PXR

- SJW
- gugulipid
- hops
- others?

These herbs are predicted to interact with many drugs
PXR Assays Predict Herb-Drug Interactions

- Reliable
- Efficient

Herb-drug interactions can be predicted and prevented
Acknowledgments

GlaxoSmithKline
Linda Moore
John Moore
Jodi Maglich
Bryan Goodwin
Tim Willson

UT Southwestern
Li Peng