Use of animal models in nutritional physiology and pathology: Studies with liver x receptor knockouts

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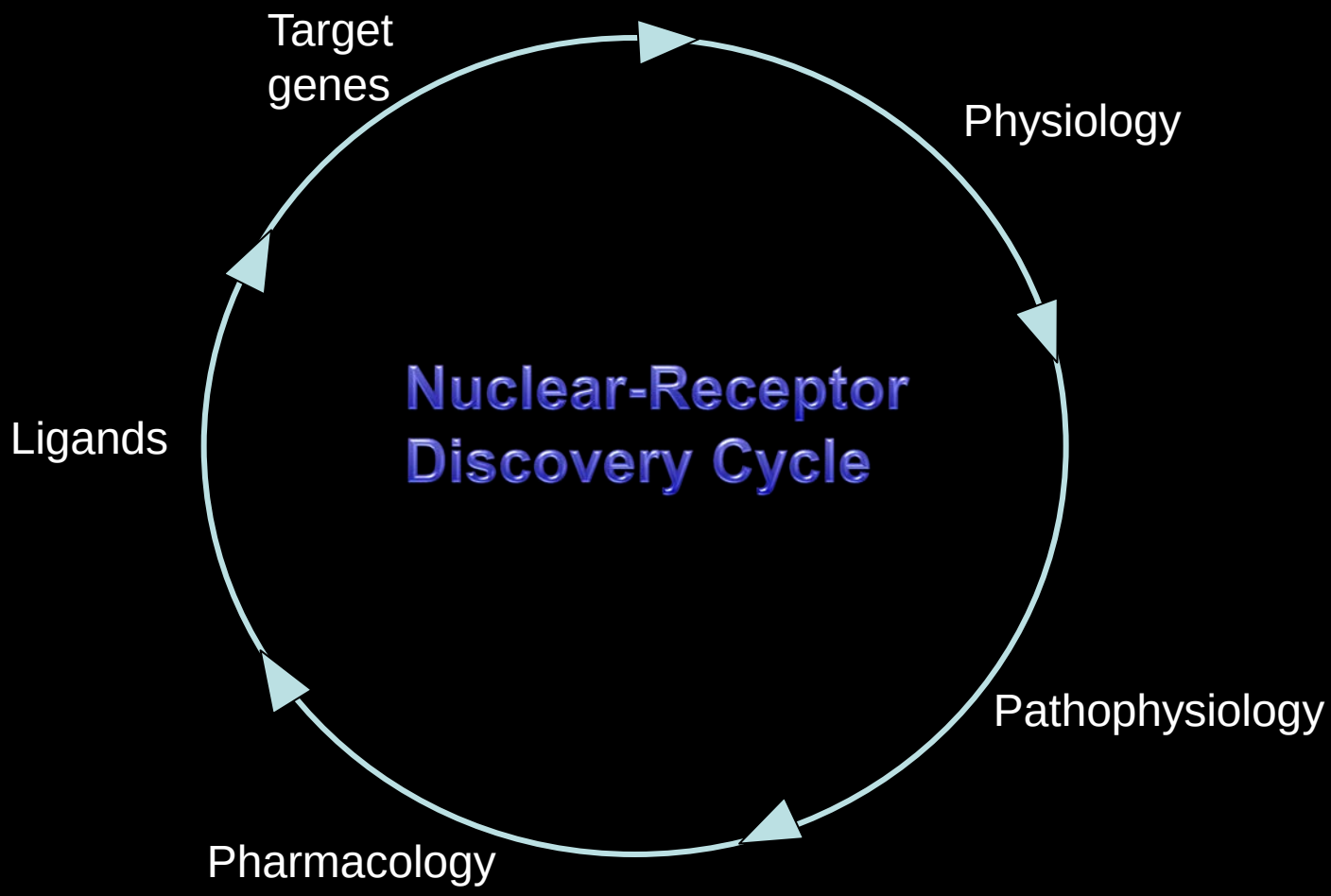
NUGO Week 2011

Animal models important for all steps



Shulman, A. et al. NEJM (2005)

Nuclear hormone receptors

Steroid Sisters

(Endocrine Receptors)

GR	*glucocorticoid*
MR	*mineralocorticoid*
PR	*progesterone*
AR	*androgen*
ERα,β	*estrogen*

RARα,β,γ	*retinoic acid*
TRα,β	*thyroid hormone*
VDR	*vitamin D, LCA*

Orphan Brothers

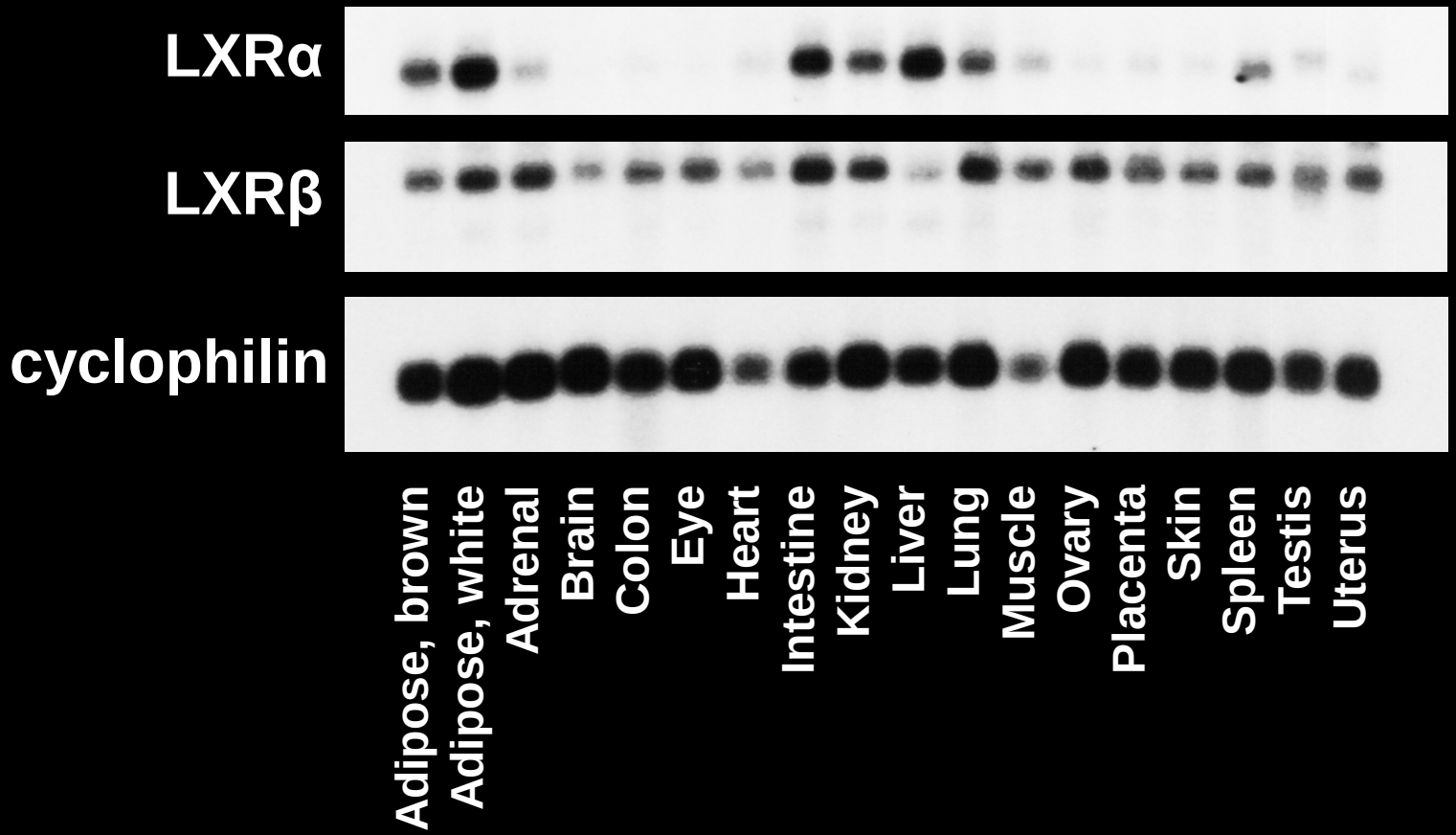
(Lipid-sensing Receptors)

RXRα,β,γ	*9cRA, DHA*
PPARα,δ,γ	*prostanoids, FA*
LXRα,β	*oxysterols*
FXR	*bile acids*
PXR/SXR	*xenobiotics*
CAR	*xenobiotics*

(Up for Adoption)

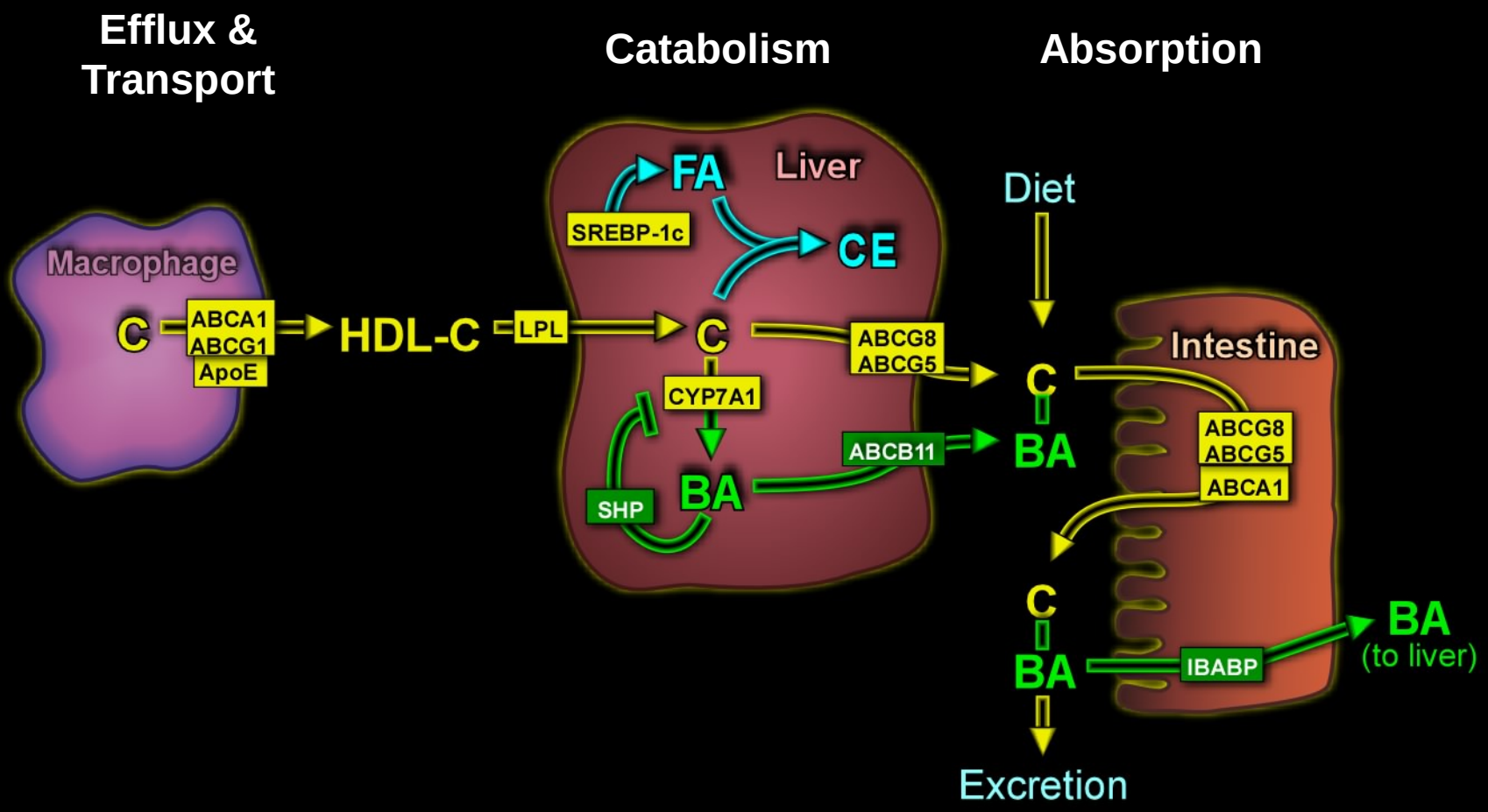
SF-1
LRH-1
DAX-1
SHP
TLX
PNR
GCNF
TR 2,4
HNF-4α,γ
RORα,β,γ
RVRα,β
NGFI-Bα,β,γ
COUP-TFα,β,γ
ERRα,β,γ

LXRα and LXRβ tissue distribution



J.J. Repa

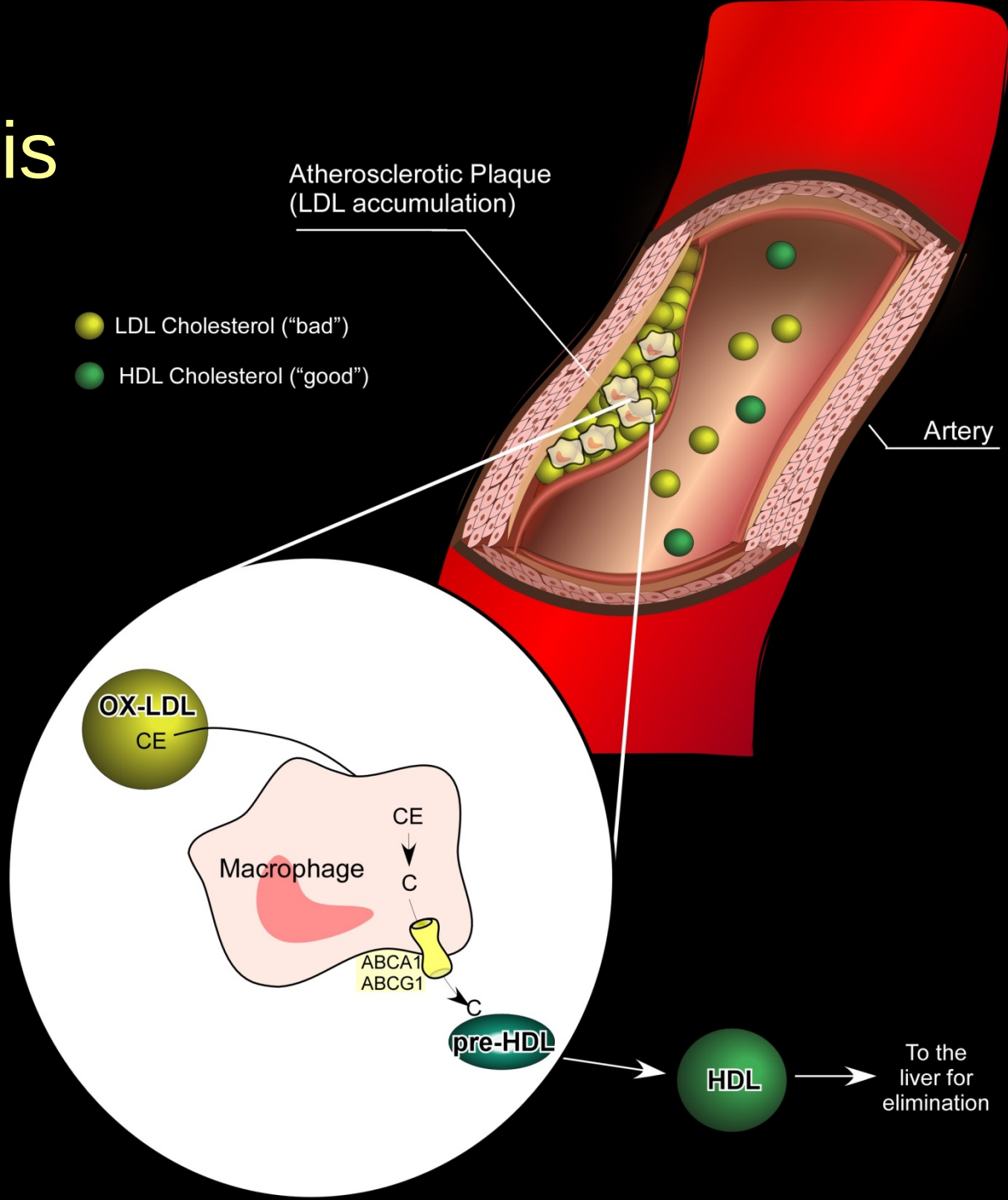
LXRs in cholesterol homeostasis



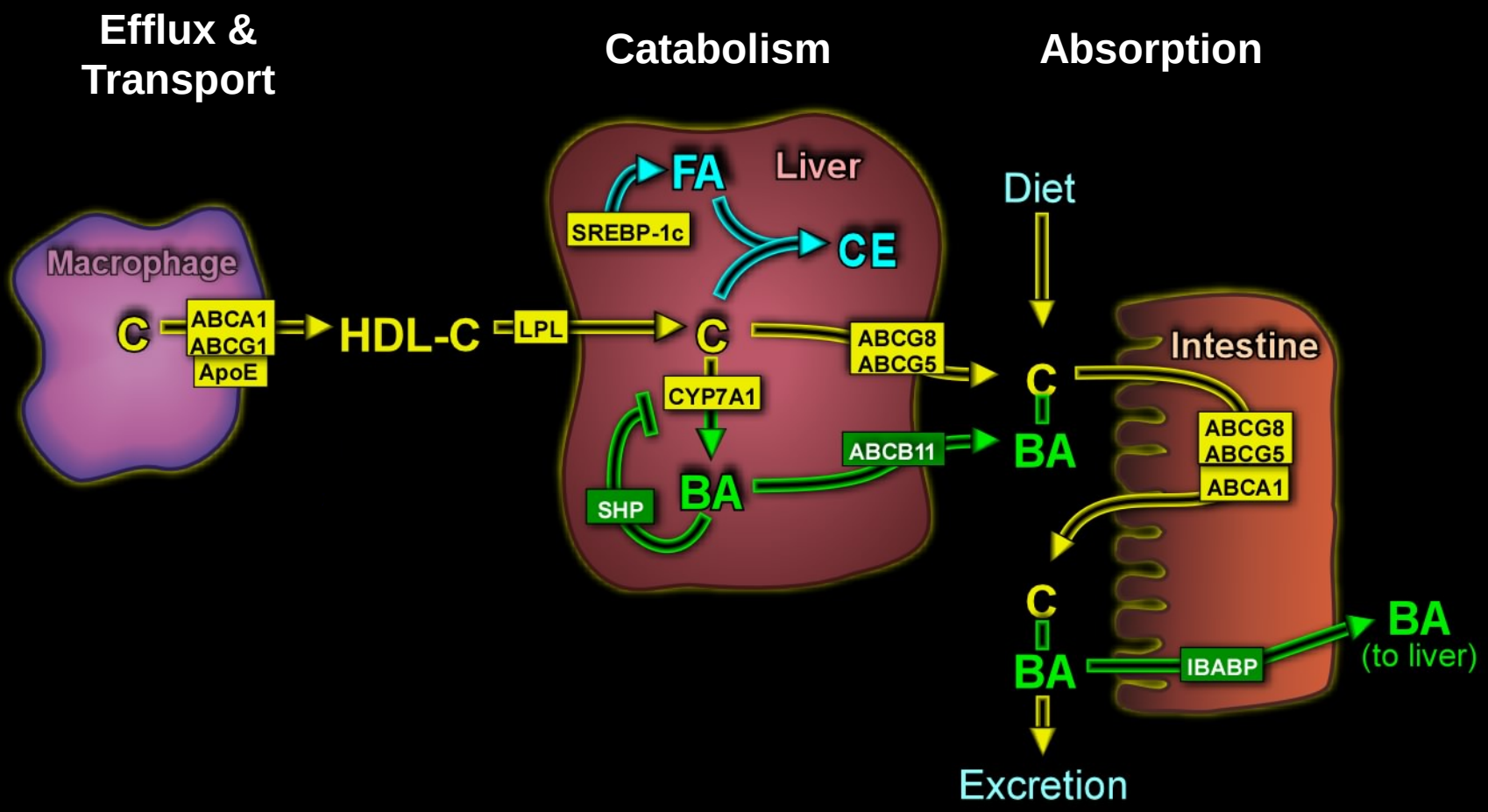
LXRs and atherosclerosis

↑ Reverse cholesterol transport

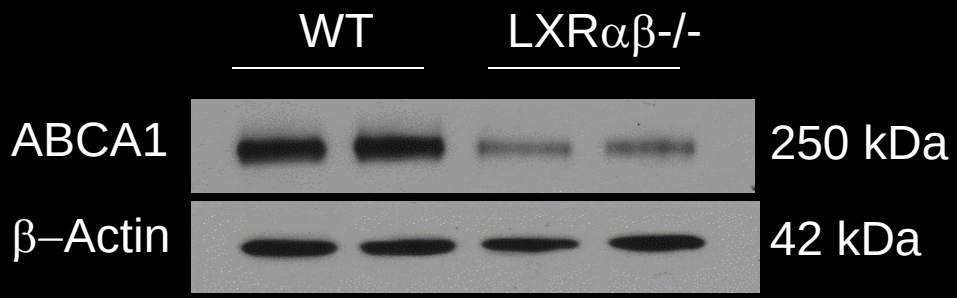
↓ Inflammation



LXRs in cholesterol homeostasis

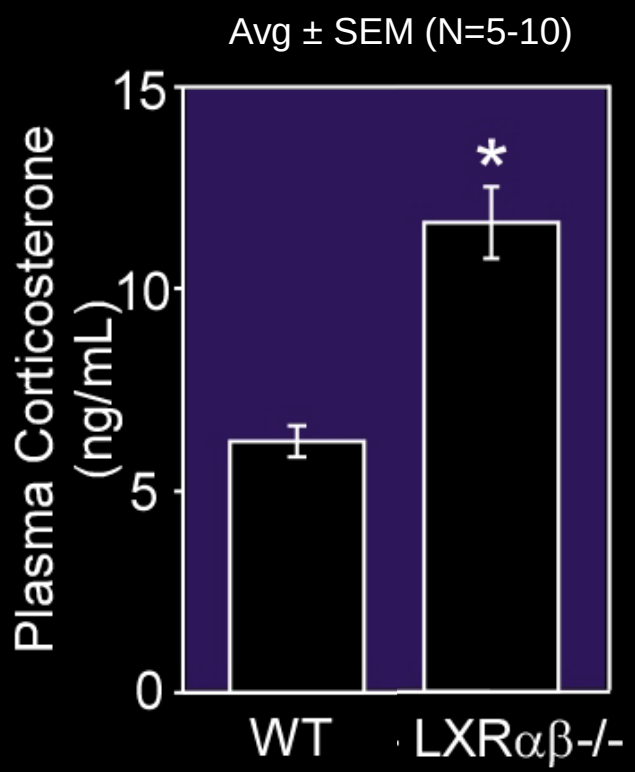


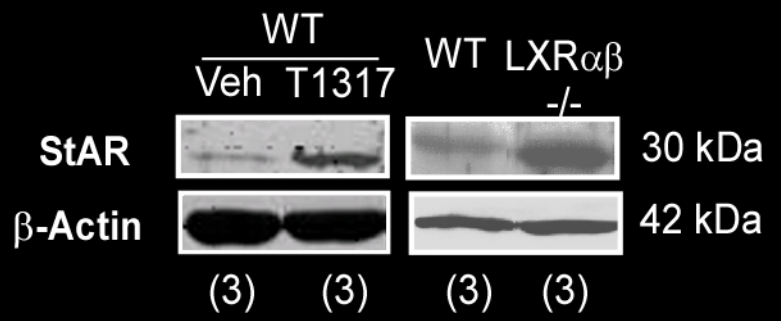
Chronic stress: high-fat diet

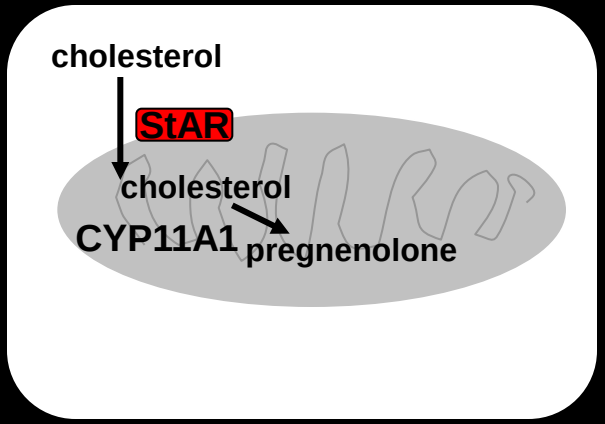


Cummins et al. JCI (2006)

Hypercorticosteronemia in LXRα/β-/-





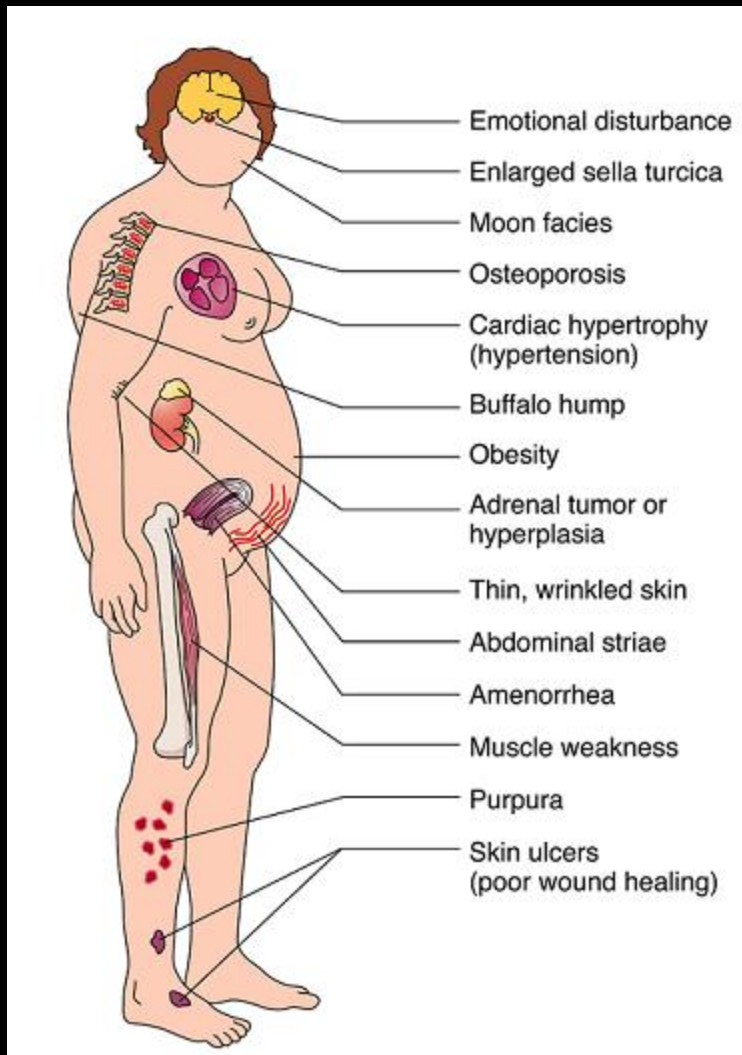


Cummins et al. JCI (2006)

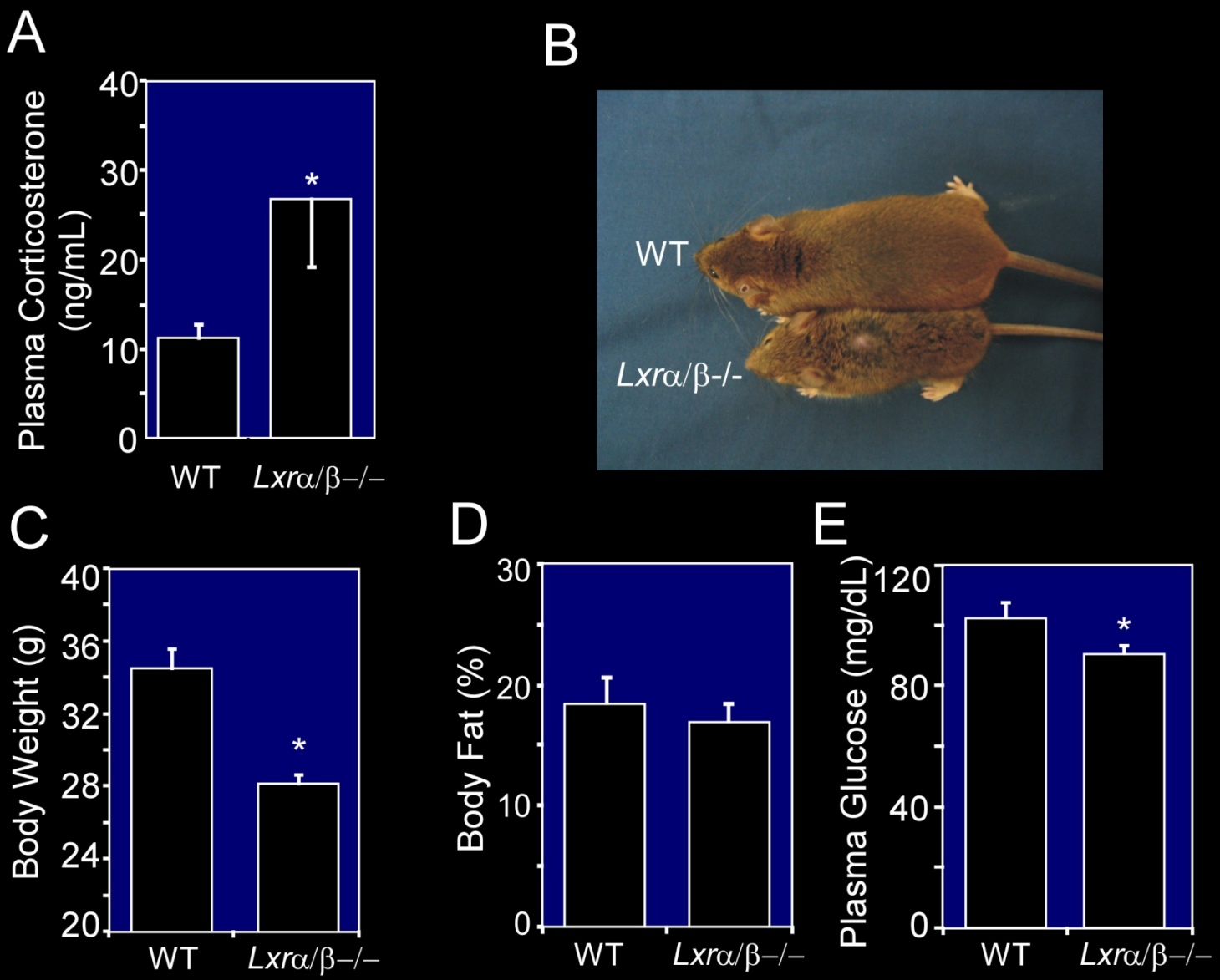
Cushing's syndrome

Cortisol excess

- General
  - Obesity
  - Hypertension
- Metabolic
  - Diabetes or impaired glucose tolerance
  - Hyperlipidemia
  - Kidney stones
  - Polyuria
- Musculoskeletal
  - Osteopenia or osteoporosis
  - Proximal myopathy
- Immune Suppression



LXR-null mice are not Cushing-like

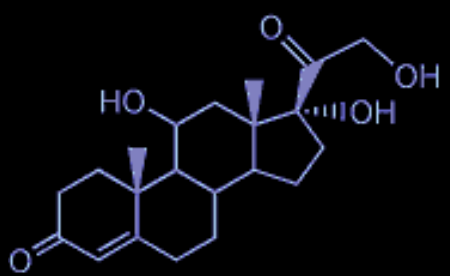


Patel et al. JCI (2011)

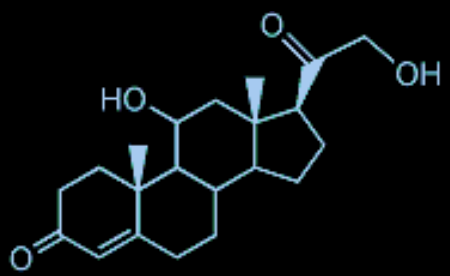
LXR KO mice lack GC phenotype

Are KO animals resistant to the effects of GCs?

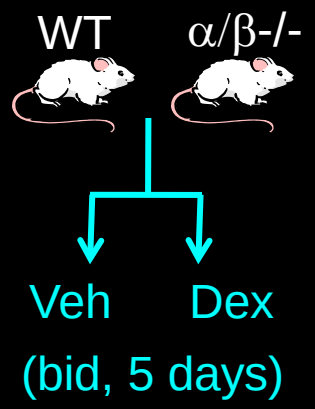
Is a 2-fold increase in corticosterone not enough to elicit Cushing's-like symptoms?



Cortisol
(humans)

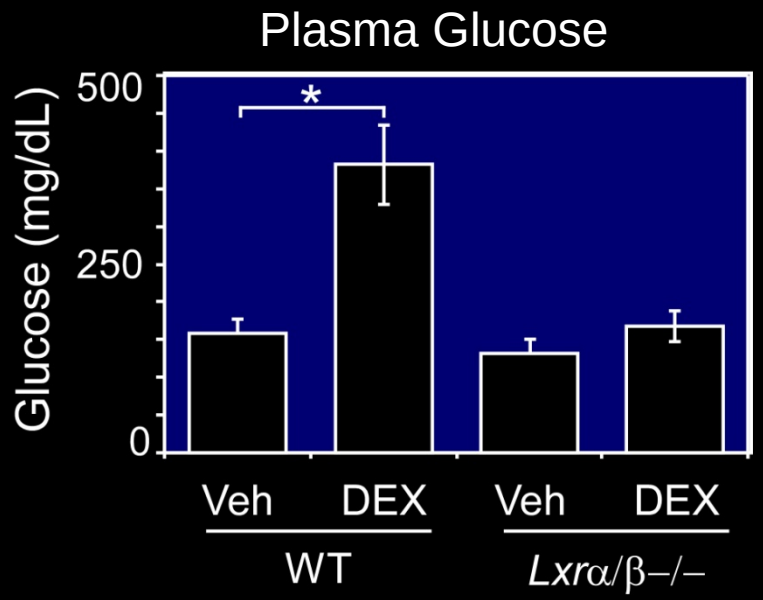


Corticosterone
(rodents)



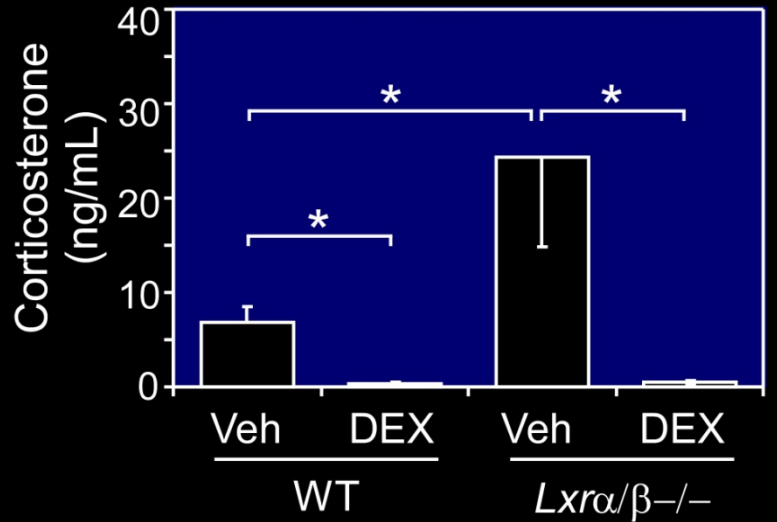
Dissociated GC effects

A

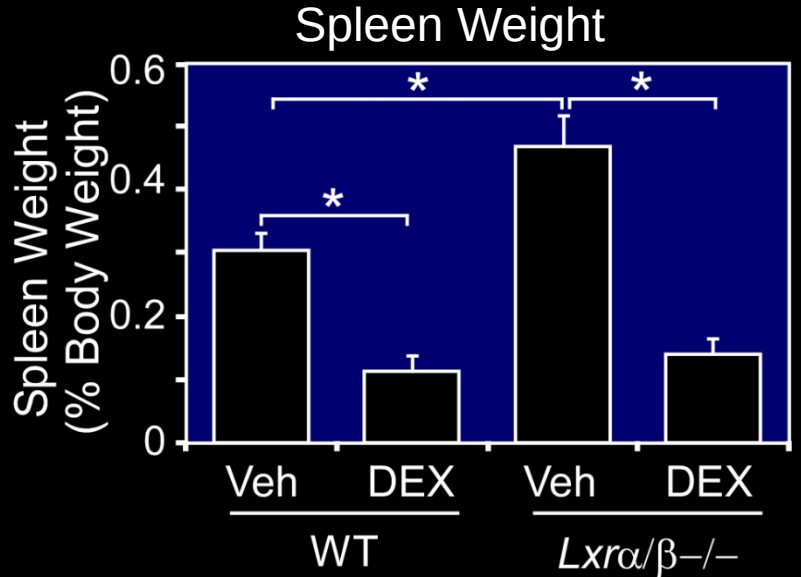


WT	KO	Glucocorticoid Effect
√	↔	↑ Gluconeogenesis

B



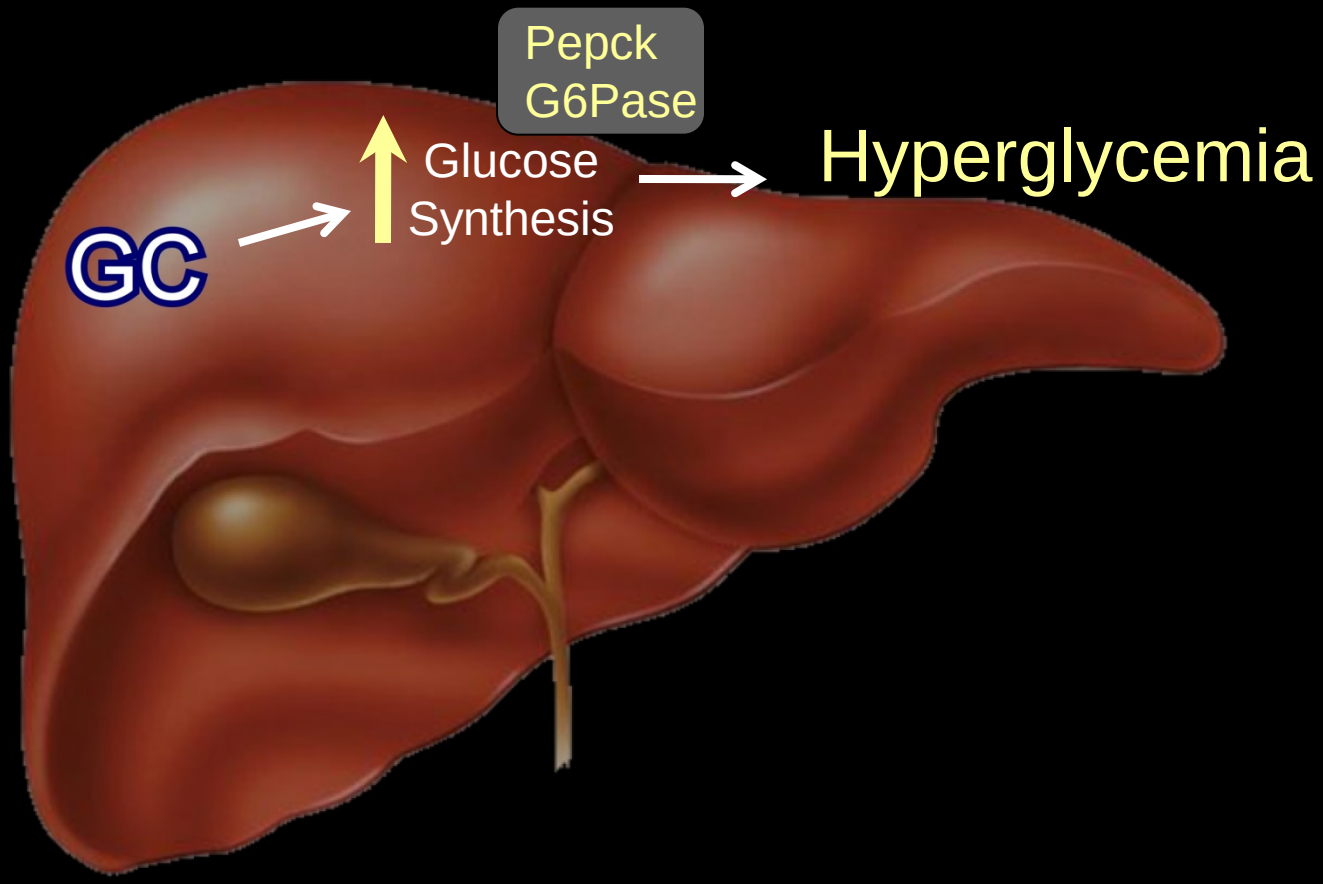
C



GCs as therapeutic agents

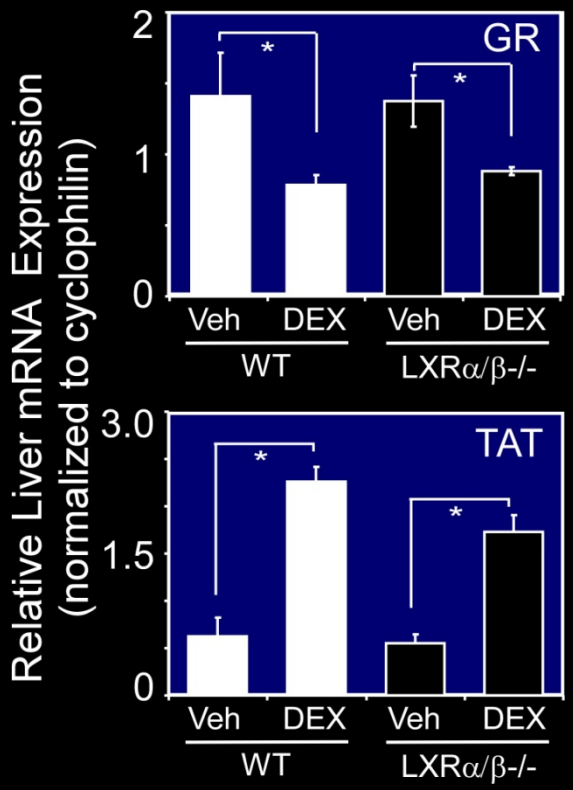
1. Synthetic glucocorticoids are among the most widely prescribed drugs in the world
2. Extensively used for their anti-inflammatory and immunosuppressive properties
3. Used to treat: rheumatoid arthritis, atopic dermatitis, cerebral edema, allergic reactions, asthma, cancer (lymphocytic leukemias and lymphomas), respiratory distress syndrome, prevent organ transplant rejection, graft-versus-host disease.
4. Side effects remain the major limitation for long-term therapeutic GCs
    1. Suppression of endogenous GC and sex steroids
    2. Osteoporosis
    3. Muscle wasting
    4. Hypertension
    5. Insulin Resistance

Actions of GCs in the liver



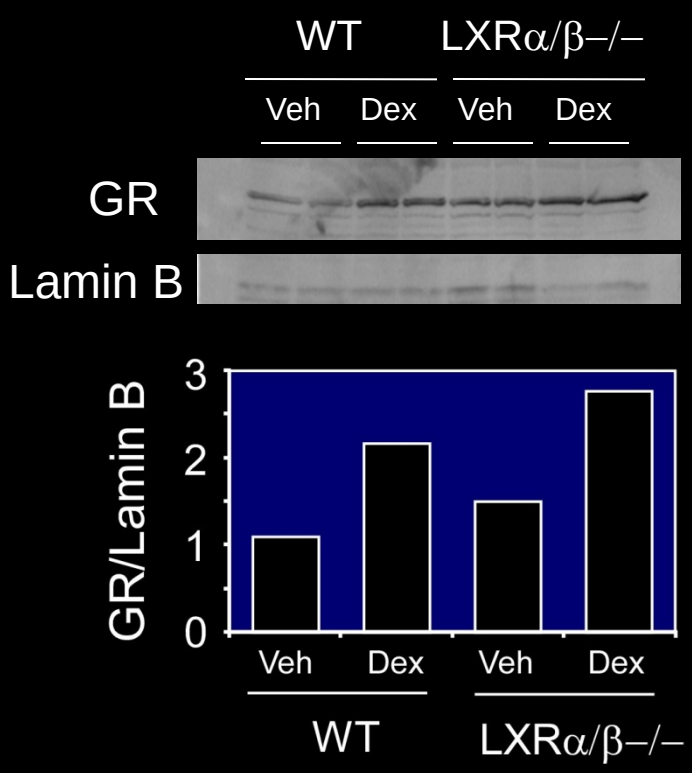
Liver Expression

mRNA



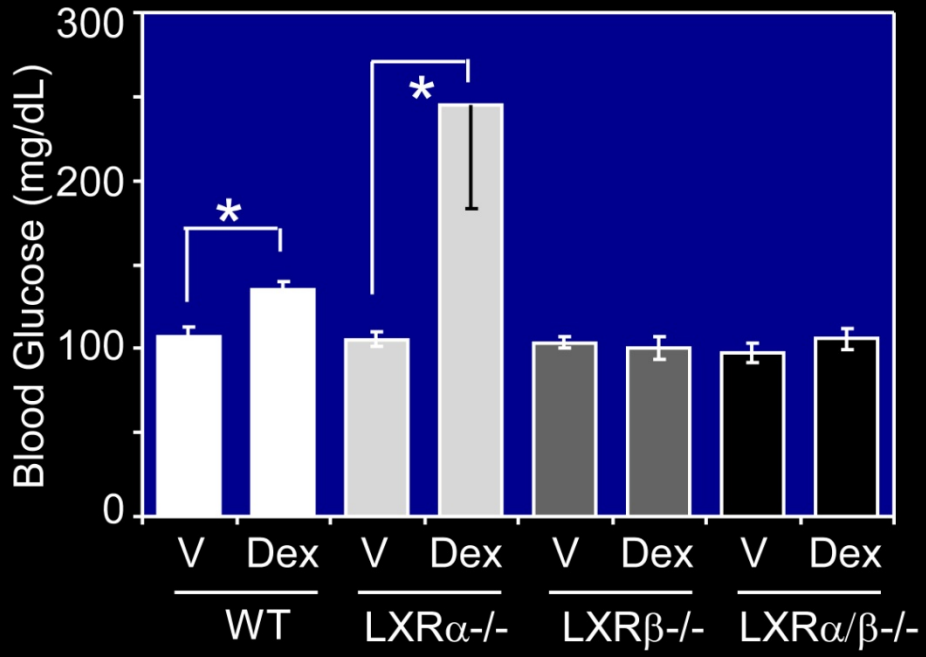
Western Blot

Liver nuclear protein



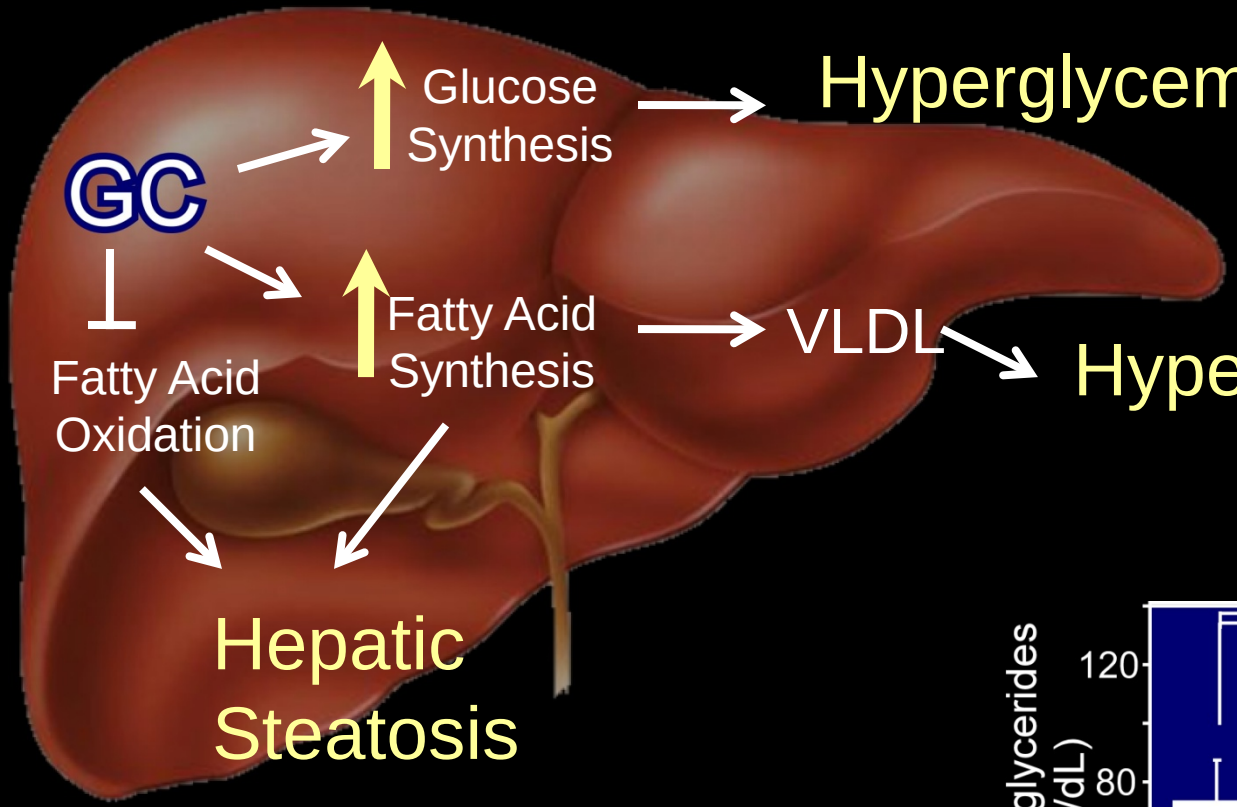
LXRβ is required for hyperglycemia

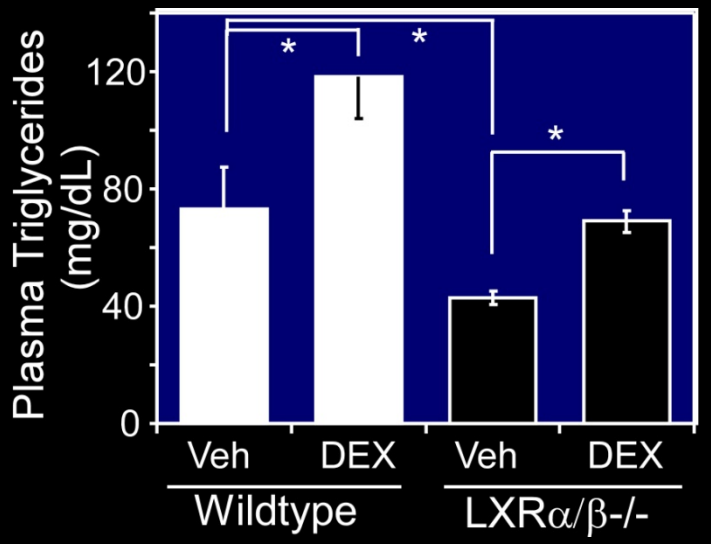
Plasma Glucose



Patel et al. JCI (2011)

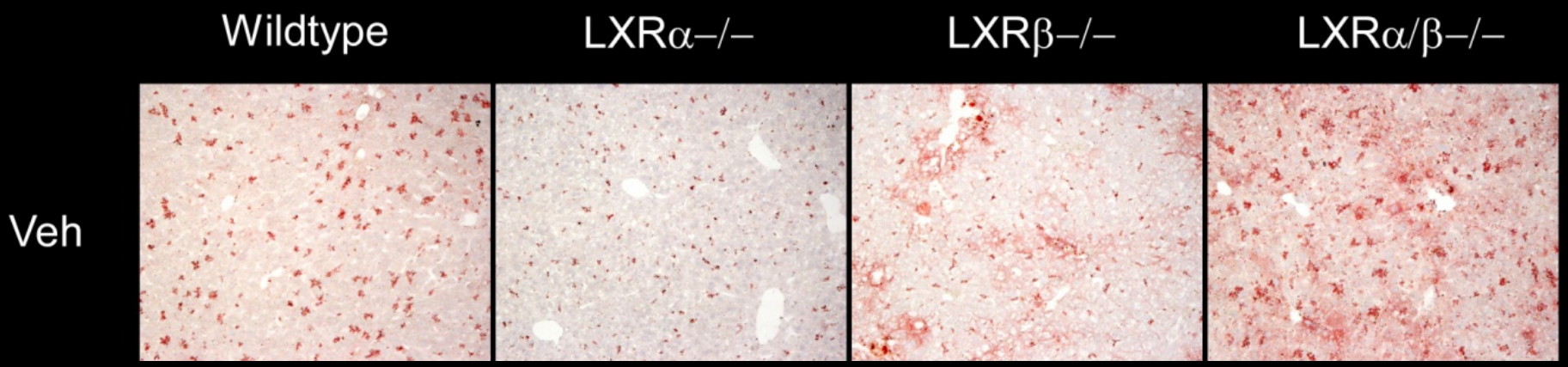
Actions of GCs in the liver





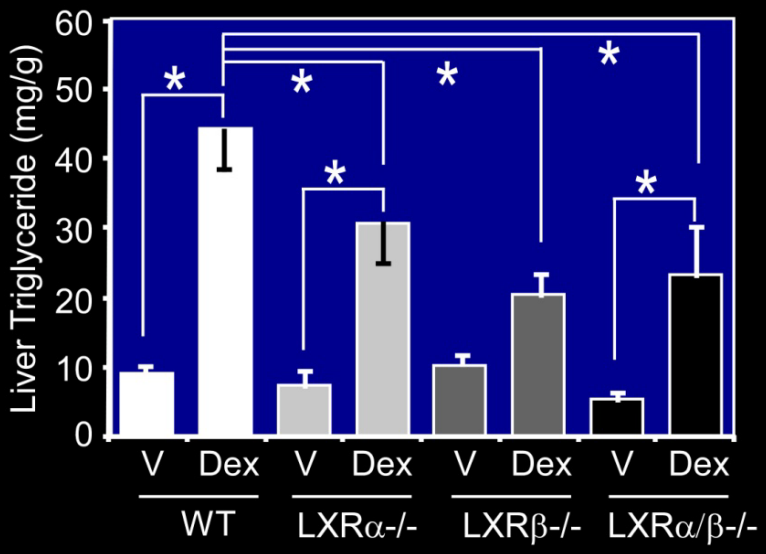
LXRβ is required for hepatosteatosis

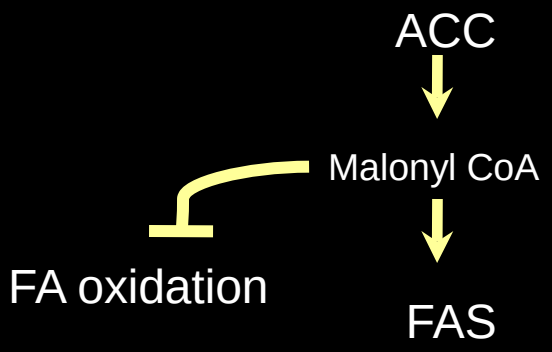
Liver Oil Red O



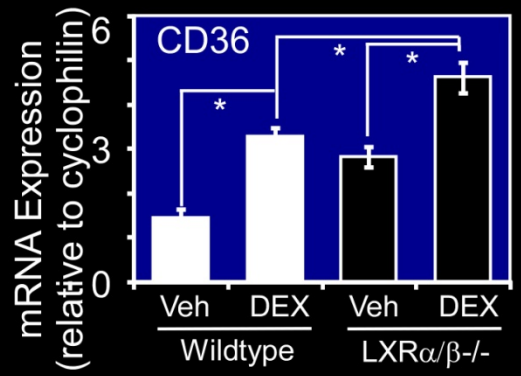
Patel et al. JCI (2011)

LXRβ is required for hepatosteatosis



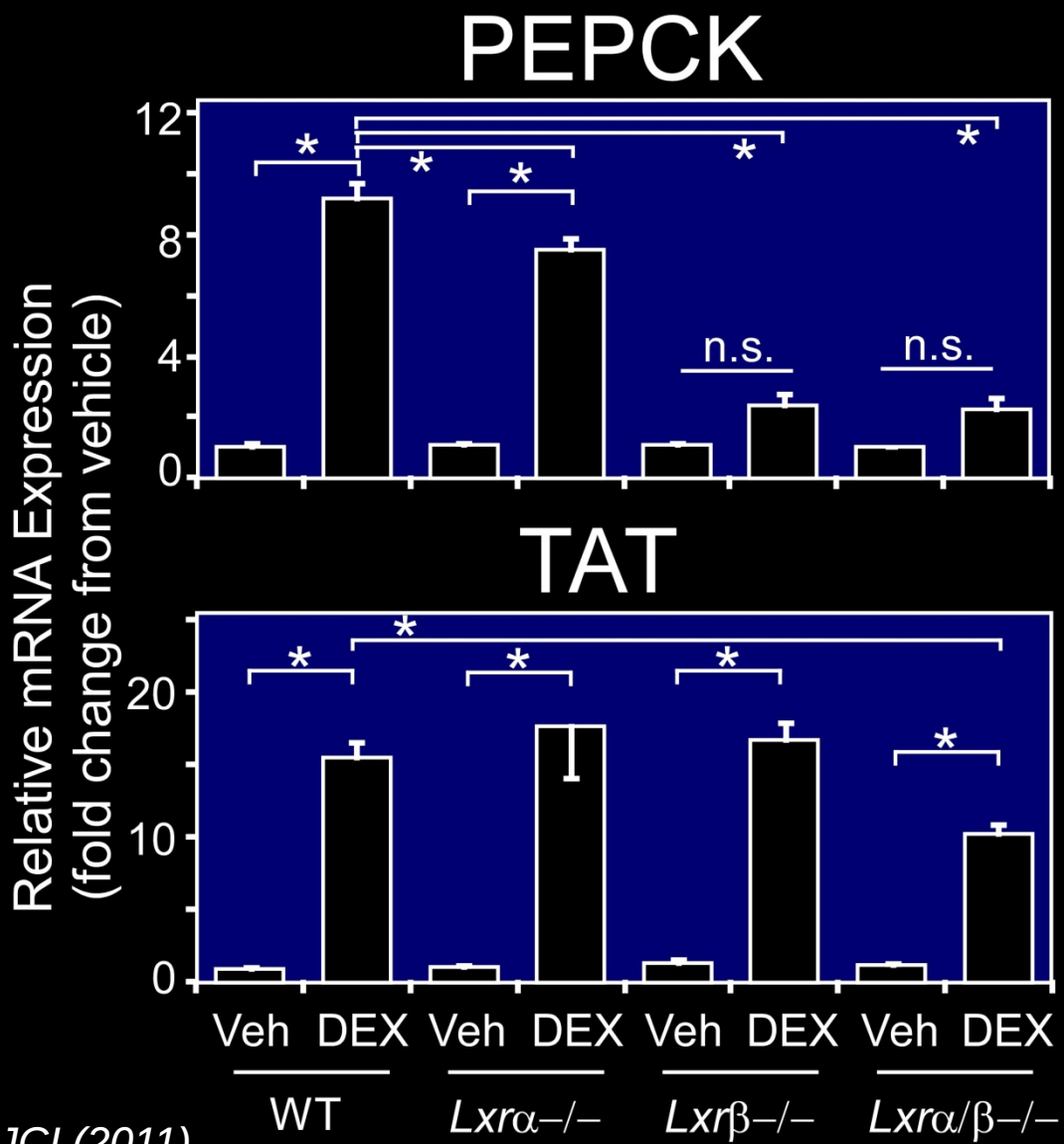


Fatty acid uptake



Are these selective GC effects liver autonomous?

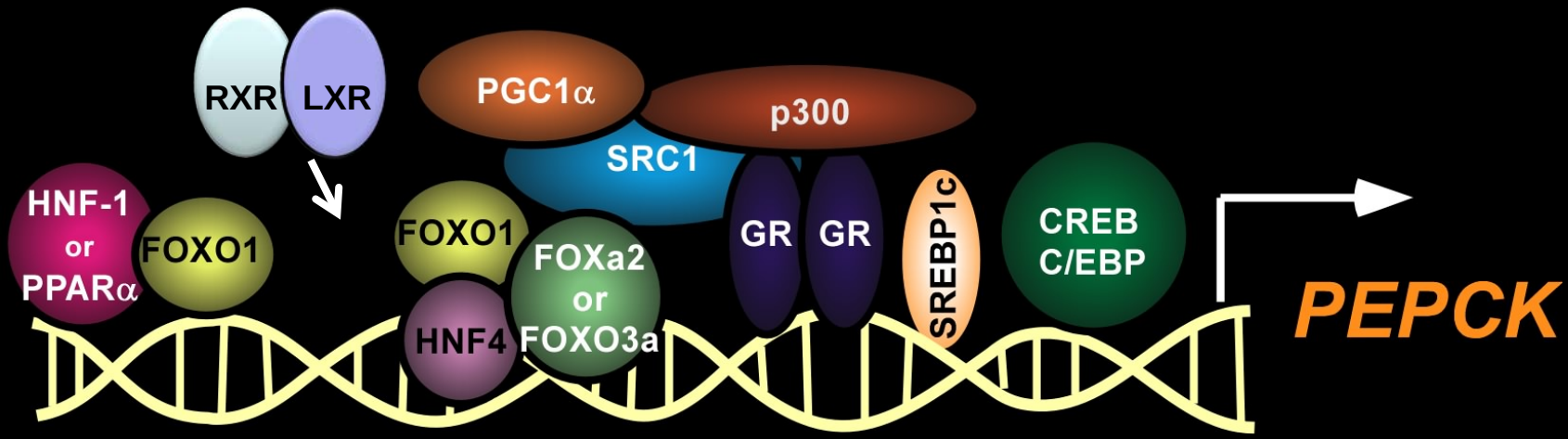
LXRβ selectively affects PEPCK



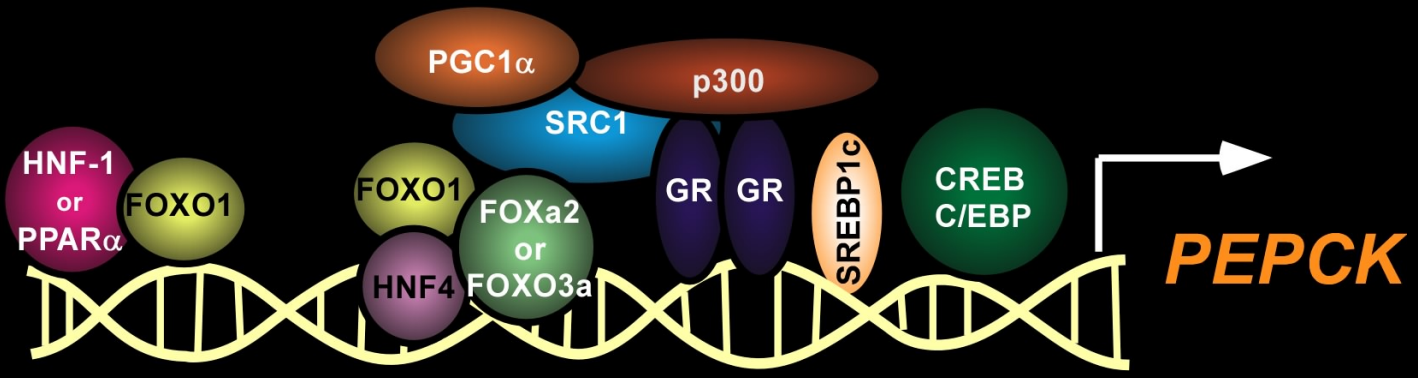
Mouse Primary Hepatocytes

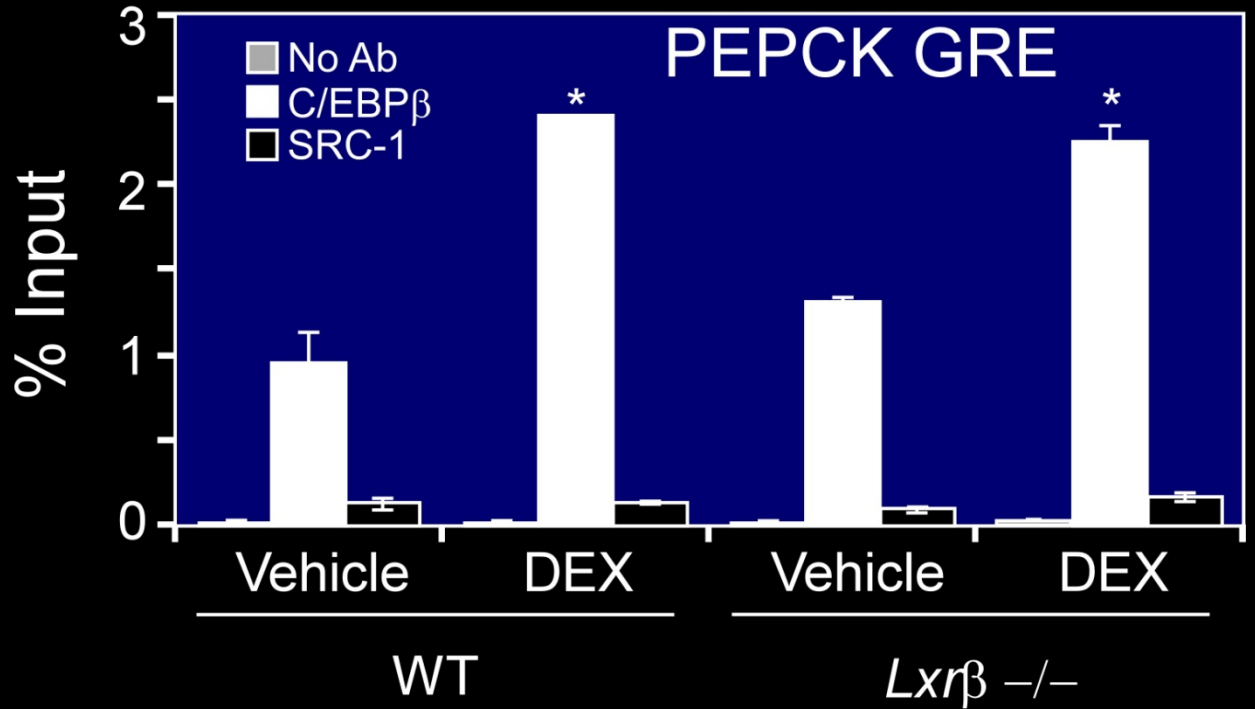
Patel et al. JCI (2011)

Where does selectively come from?



SRC-1 and C/EBPβ recruitment to PEPCK GRE are unchanged

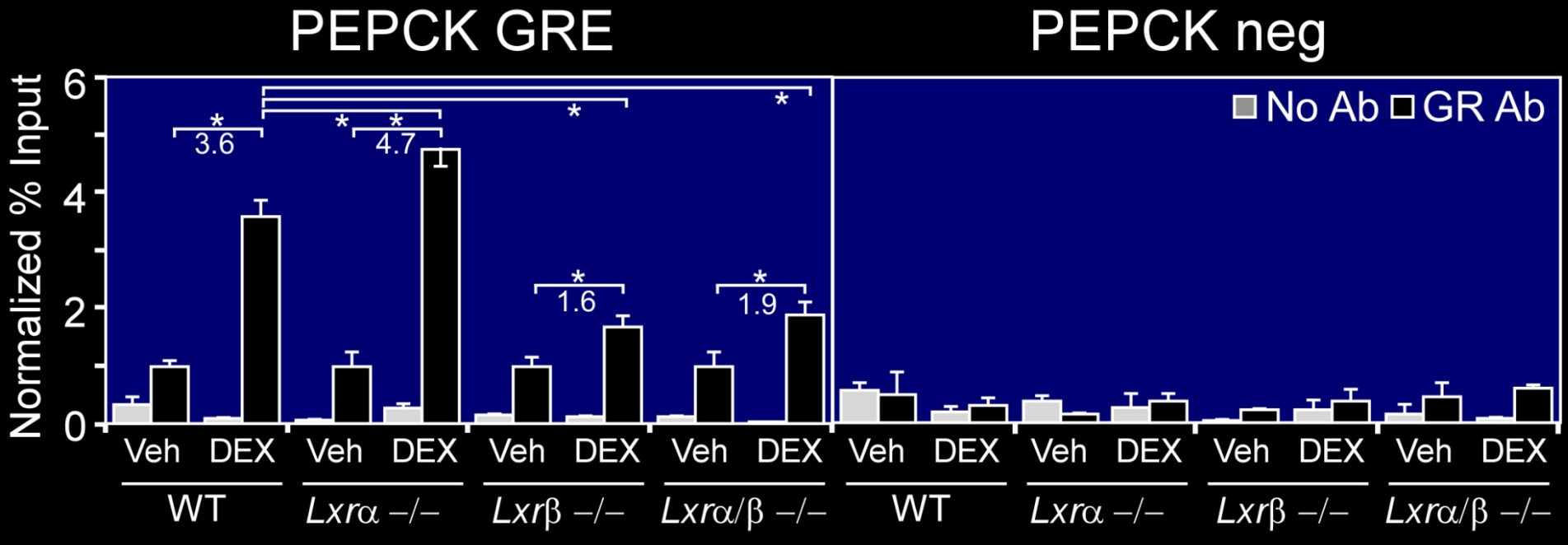




GR recruitment is selective in βKO

Chromatin Immunoprecipitation

Liver perfused with 10nM Dex 30 mins



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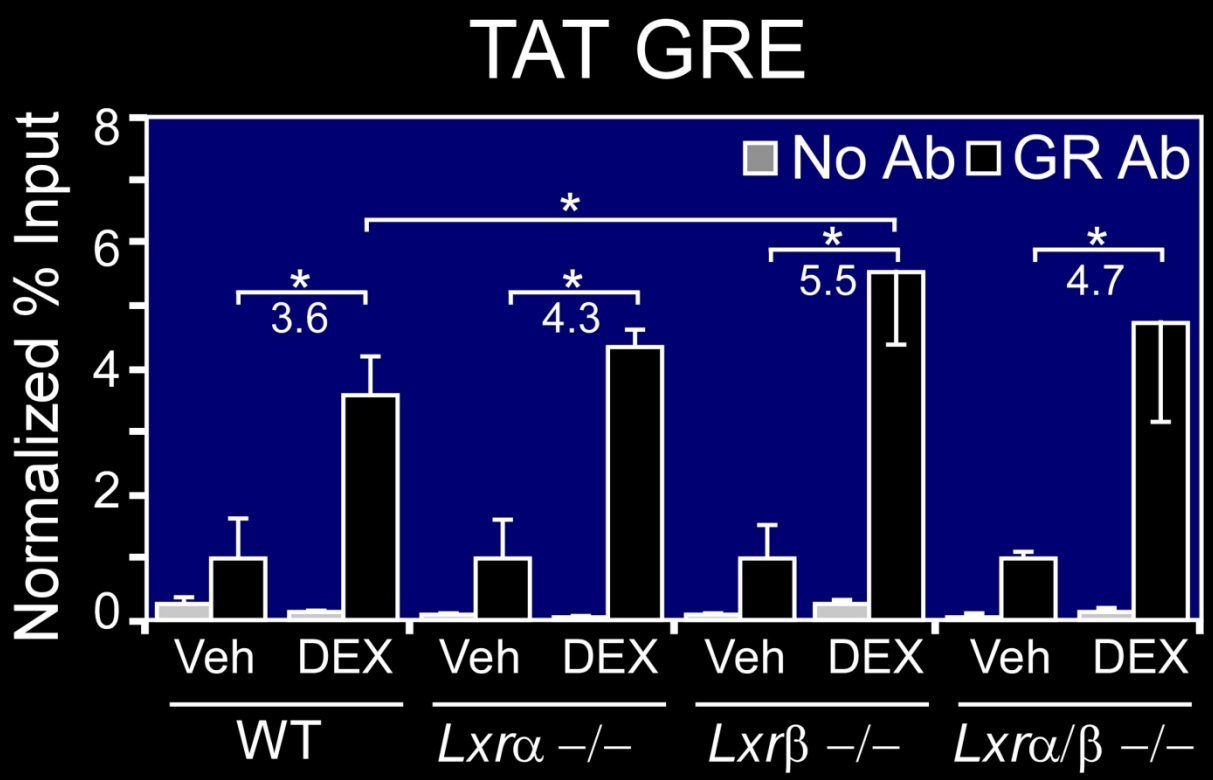
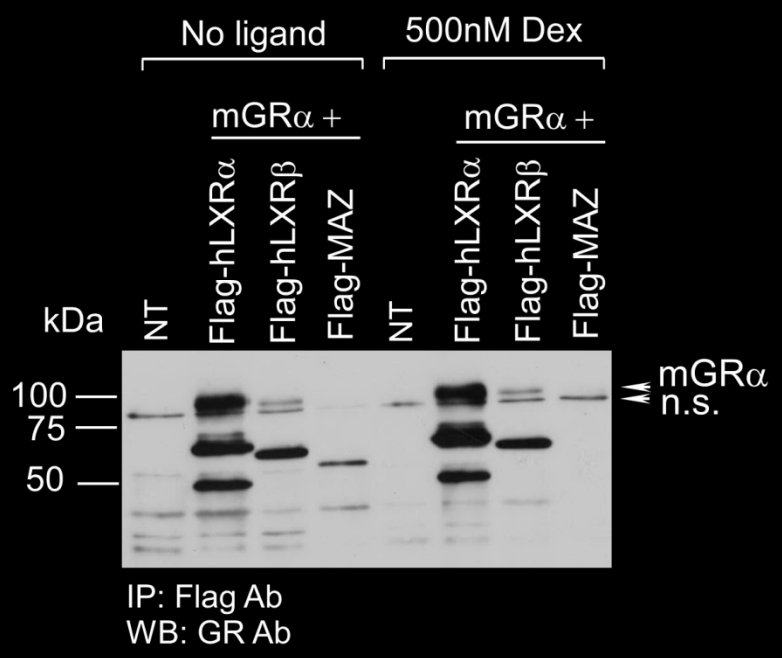
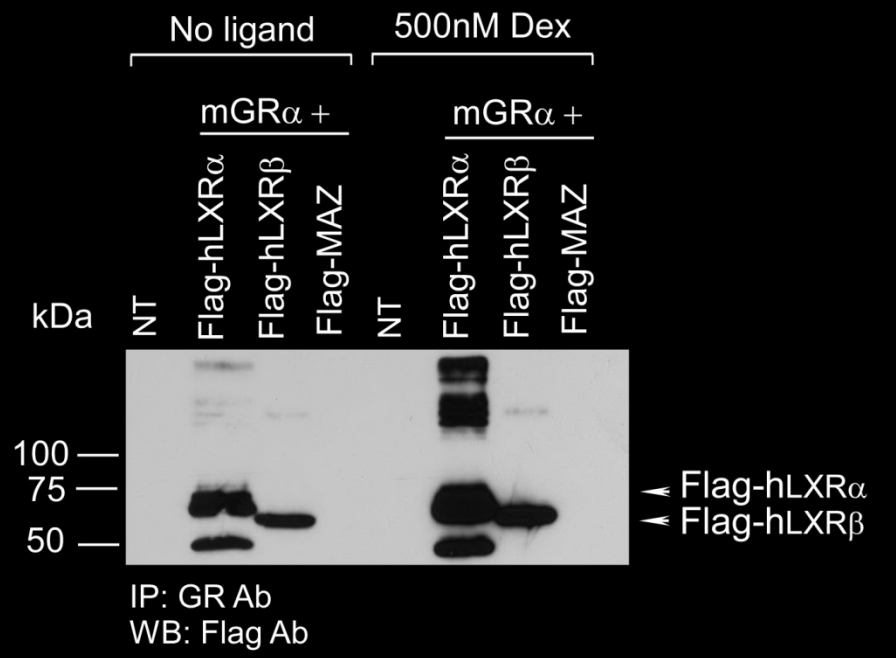
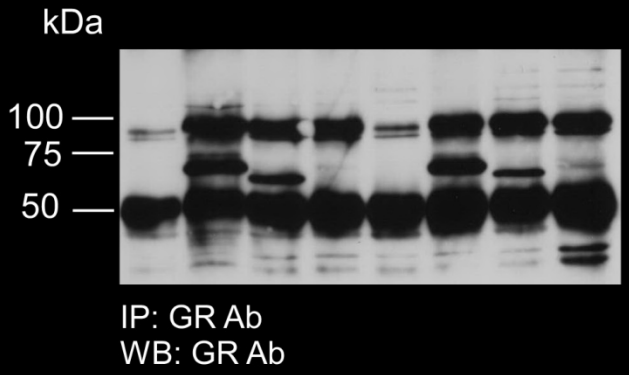


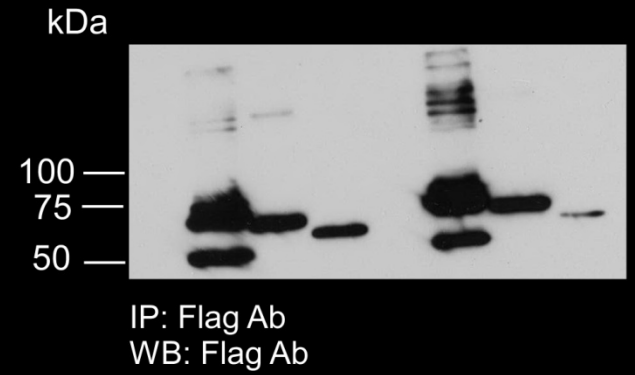
Both LXRα and LXRβ Co-IP with GR

Molecular weight of proteins:
GRα - 90kDa
LXRα - 50kDa
LXRβ - 56kDa
MAZ - 55kDa



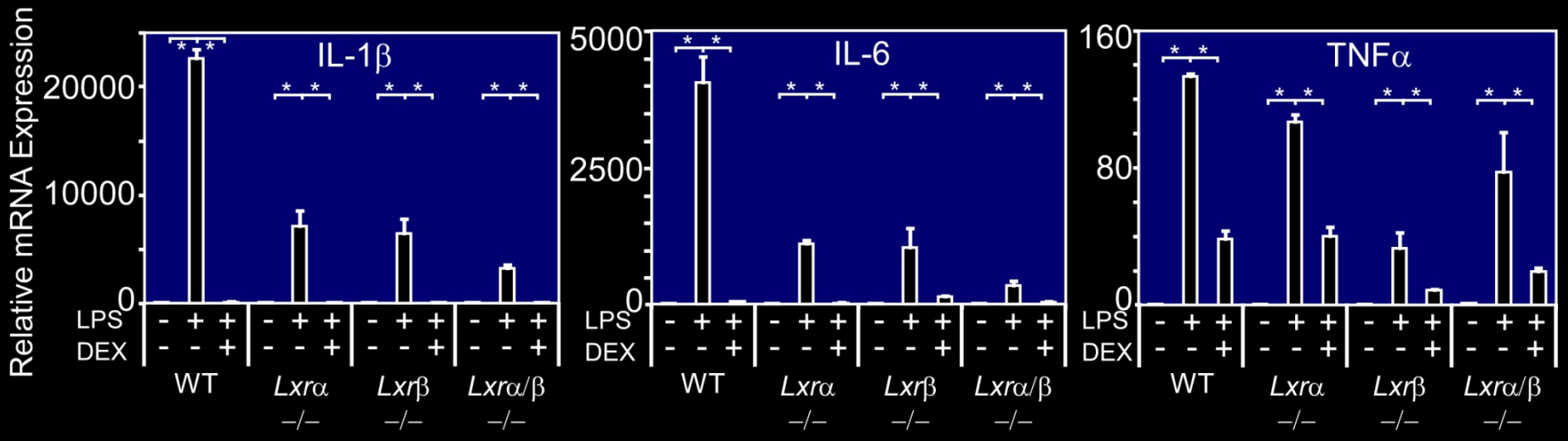






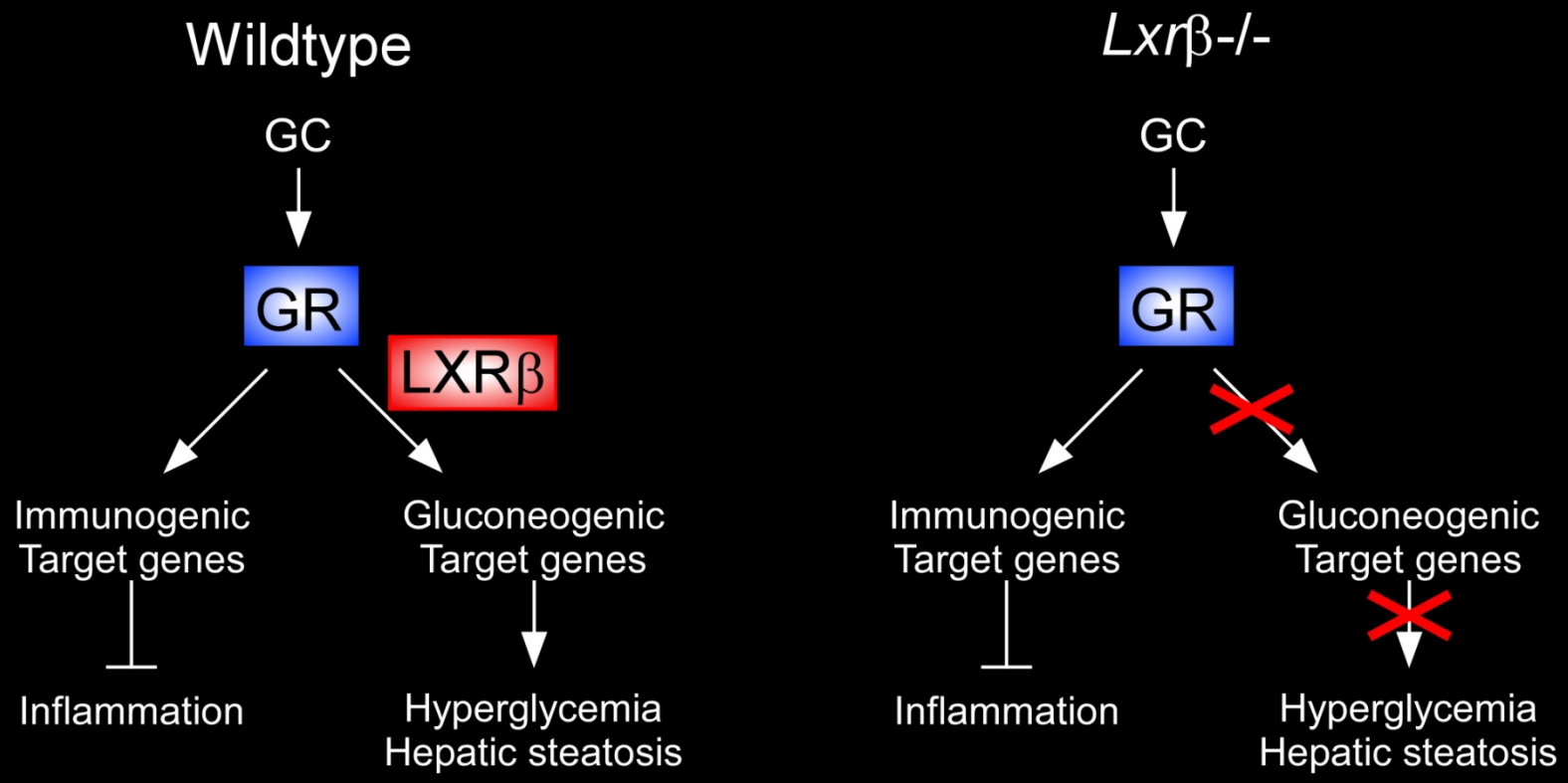
LXRβ-/- are sensitive to GC-induced immunosuppression

Primary Mouse Peritoneal Macrophages



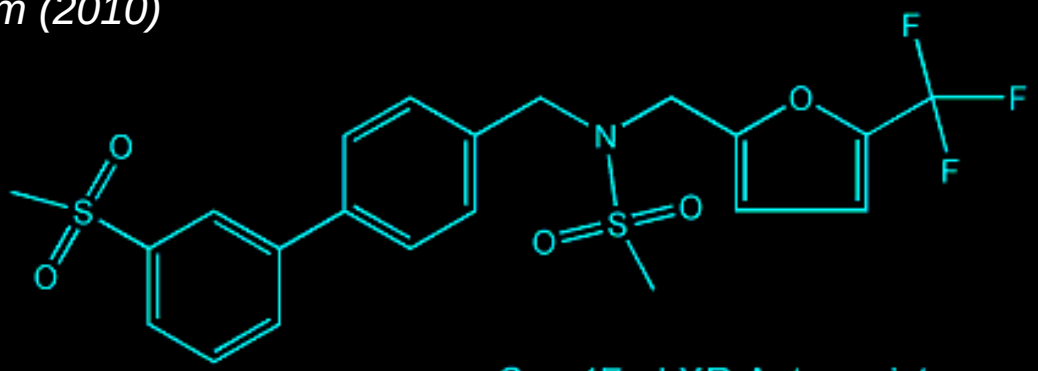
Pre-treat 6 hr with Veh or Dex (10nM)
Stimulate with 100ng/mL LPS

Working Model



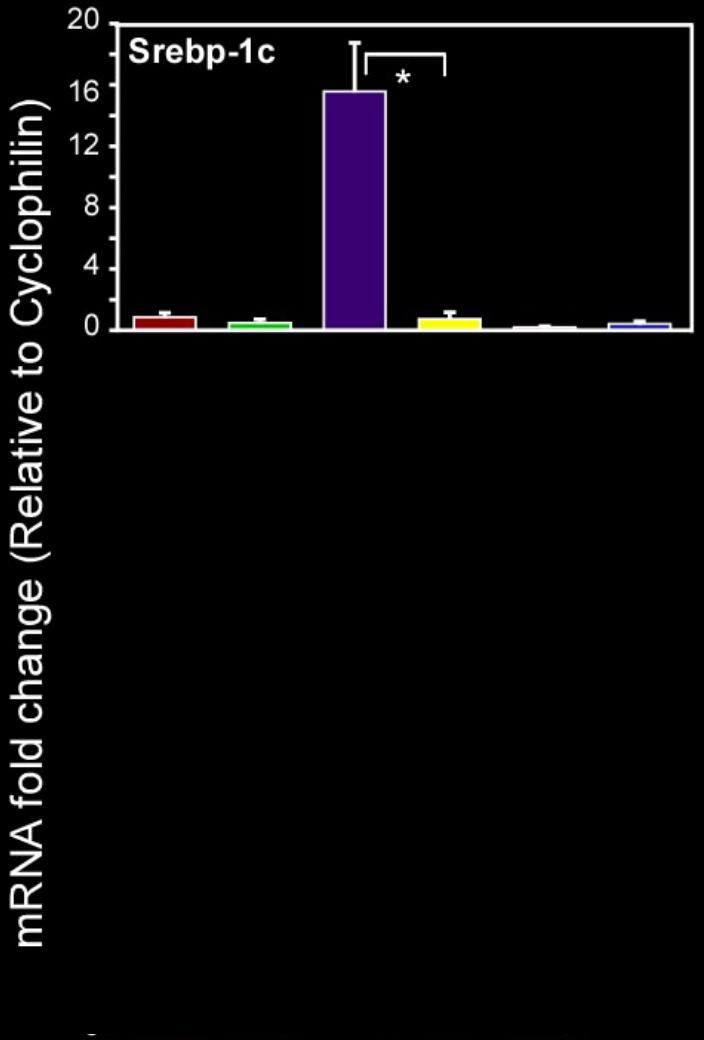
Would an LXR antagonist disrupt interaction?

Zuercher et al. J Med Chem (2010)



Cmp17 - LXR Antagonist

LXRβ antagonist mimics loss of function



LXRα–/– Primary Hepatocytes

Summary and Implications for “Health”

- Chronic dietary stress can increase corticosterone levels by altering adrenal homeostasis

- Persistent elevated corticosterone (signaling through GR) co-operates with liver LXRβ to induce a gluconeogenic program

- I agree with the definition of health as defined in ecology “ability to respond to perturbation within certain thresholds”. However, we also have to consider that any *sub-chronic* or *chronic* perturbations can cause detrimental re-setting of these threshold limits.

Acknowledgements

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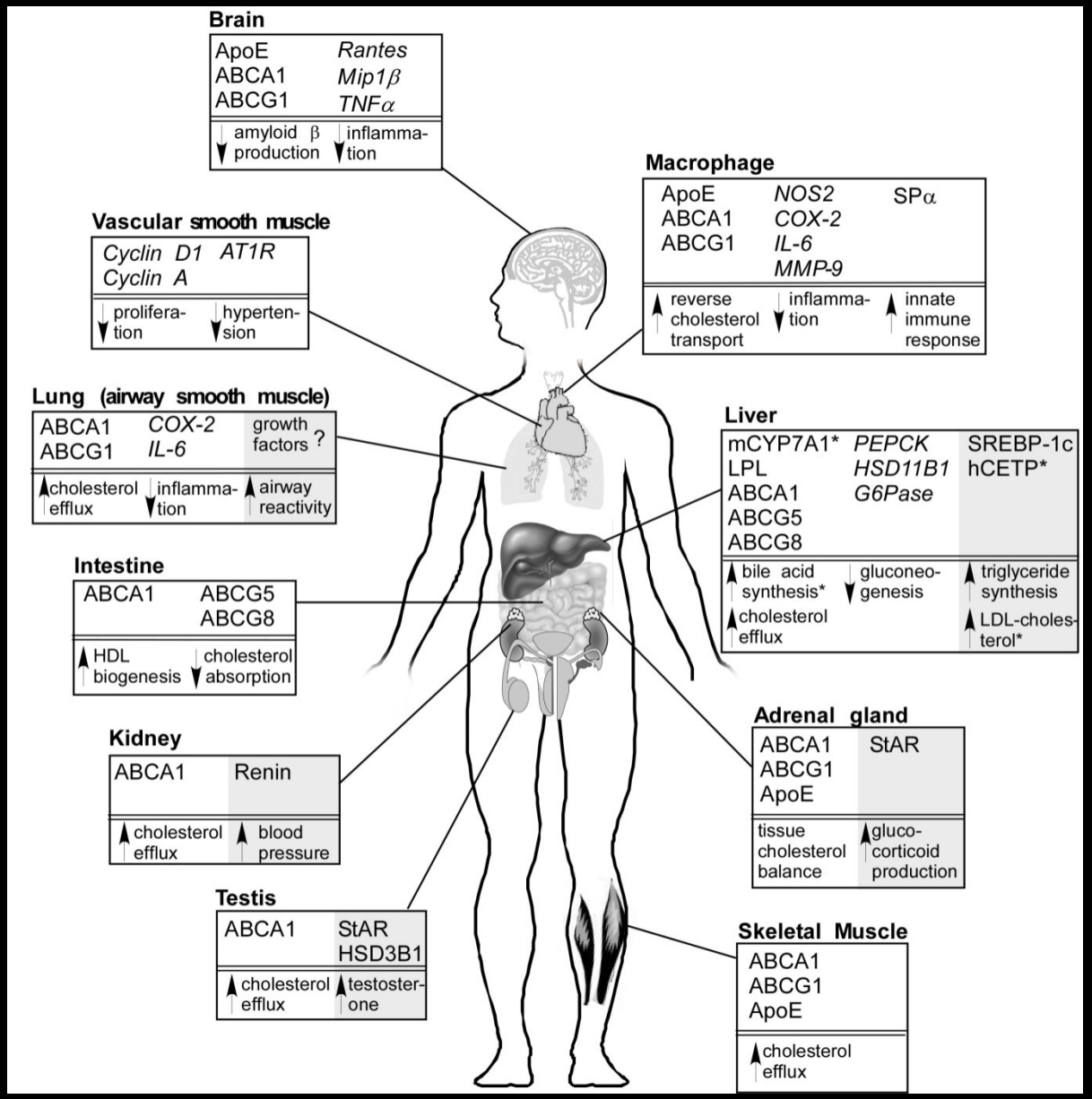
LXR tissue specific activation



Potentially beneficial for:

- Atherosclerosis
- Diabetes
- Asthma
- Diabetic nephropathy
- Alzheimer's disease

Selectivity required to avoid:

- Hypertriglyceridemia
- Hypercortisolemia
- Hypertension