Understanding the Mechanism of Action of Fibrates

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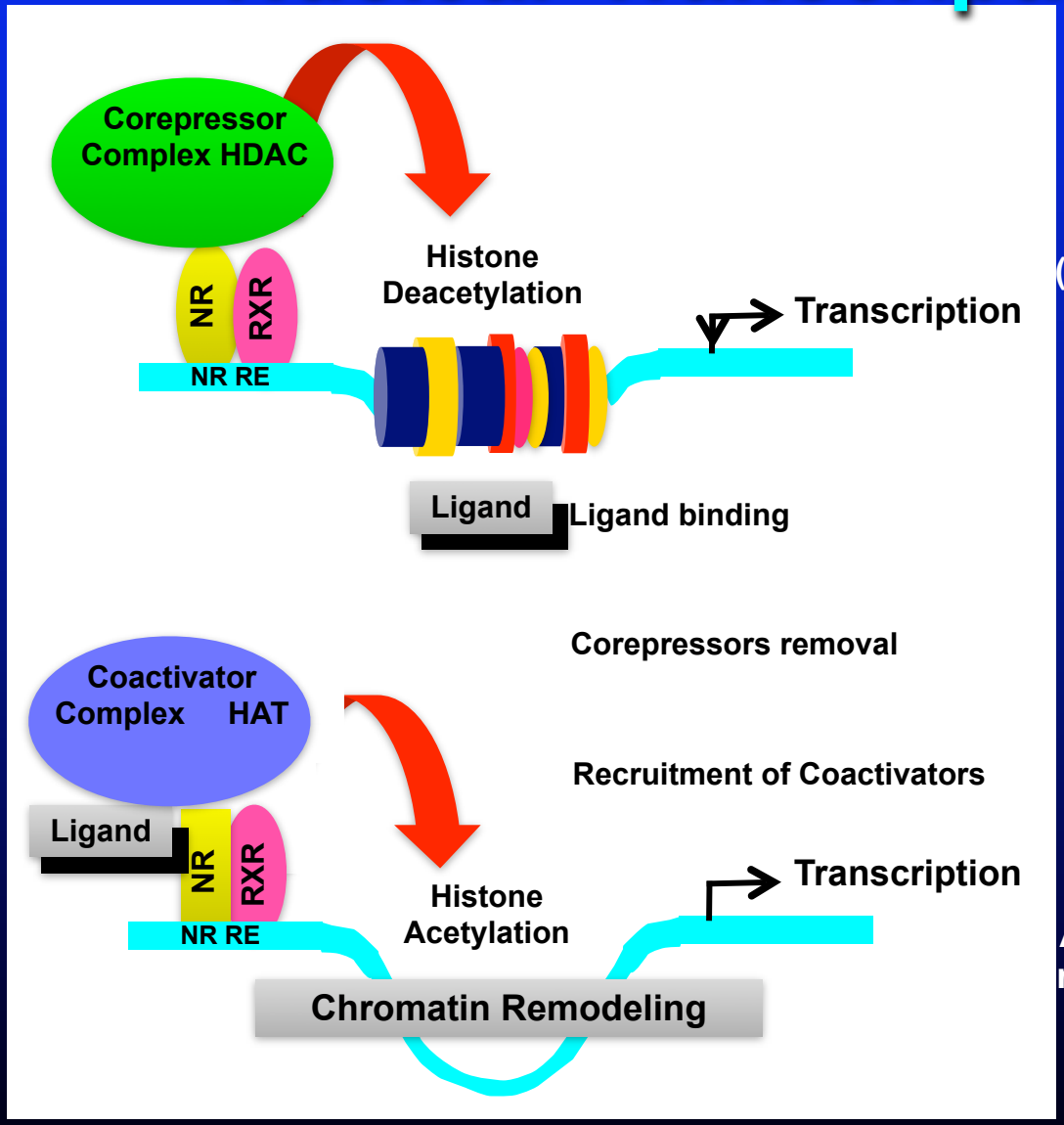
Fibrates and PPARα Agonism

Peroxisome Proliferorator-Activated Receptor α

- Peroxisome proliferator–activated receptor α (PPARα) is a ligand-activated nuclear receptor that regulates multiple genes involved with glucose and fatty acid metabolism, lipoprotein synthesis and catabolism, and vascular inflammation.
- Natural ligands include several fatty acids (saturated and unsaturated) and their derivatives, including eicosanoids.
- The PPARα/ligand complex requires heterodimerization with the retinoid X receptor/retinoic acid complex. After interaction with tissue-specific protein co-repressors or activators, the dimer attaches to distinct gene response elements, causing transcription of messenger RNA.

Dayspring T & Pokrywka G Cur Athero Rep 2006, 8:356–364

Nuclear Transcription Factors



Schematic representation of the regulation of gene transcription by nuclear receptors. In the unliganded state, nuclear receptors (NR) are bound to their specific responsive element (NRRE) generally as heterodimer with cis-retinoic acid receptor (RXR).

In this condition, heterodimers are associated with a multiprotein corepressor complex that contains histone deacetylase activity (HDAC).

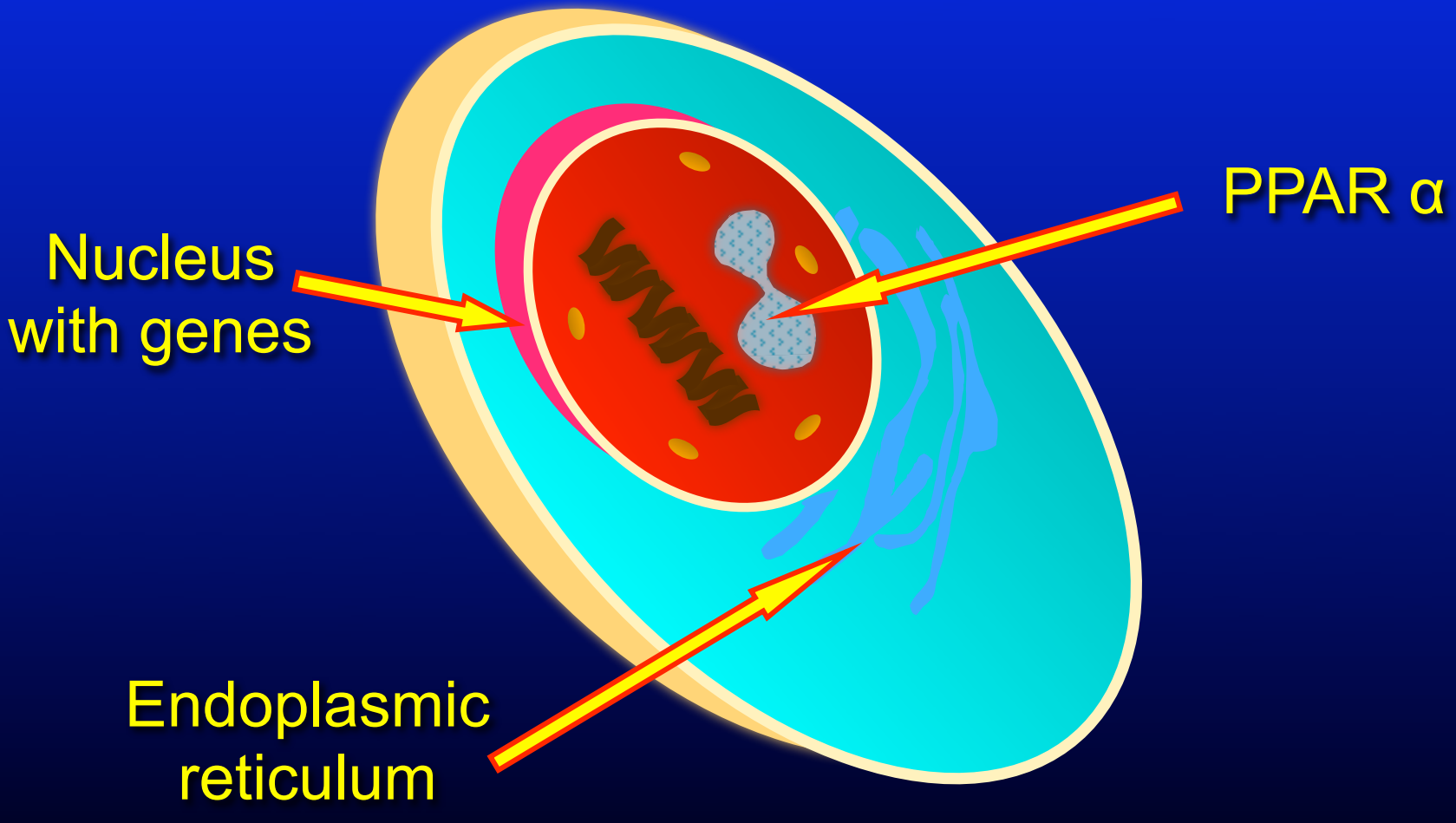
The deacetylated status of histones keeps the nucleosome in a conformation in which transcription is inhibited.

Once a ligand binds to the receptor, the corepressor complex dissociates and a coactivator complex containing histone acetyltransferase activity (HAT) is recruited to the heterodimer.

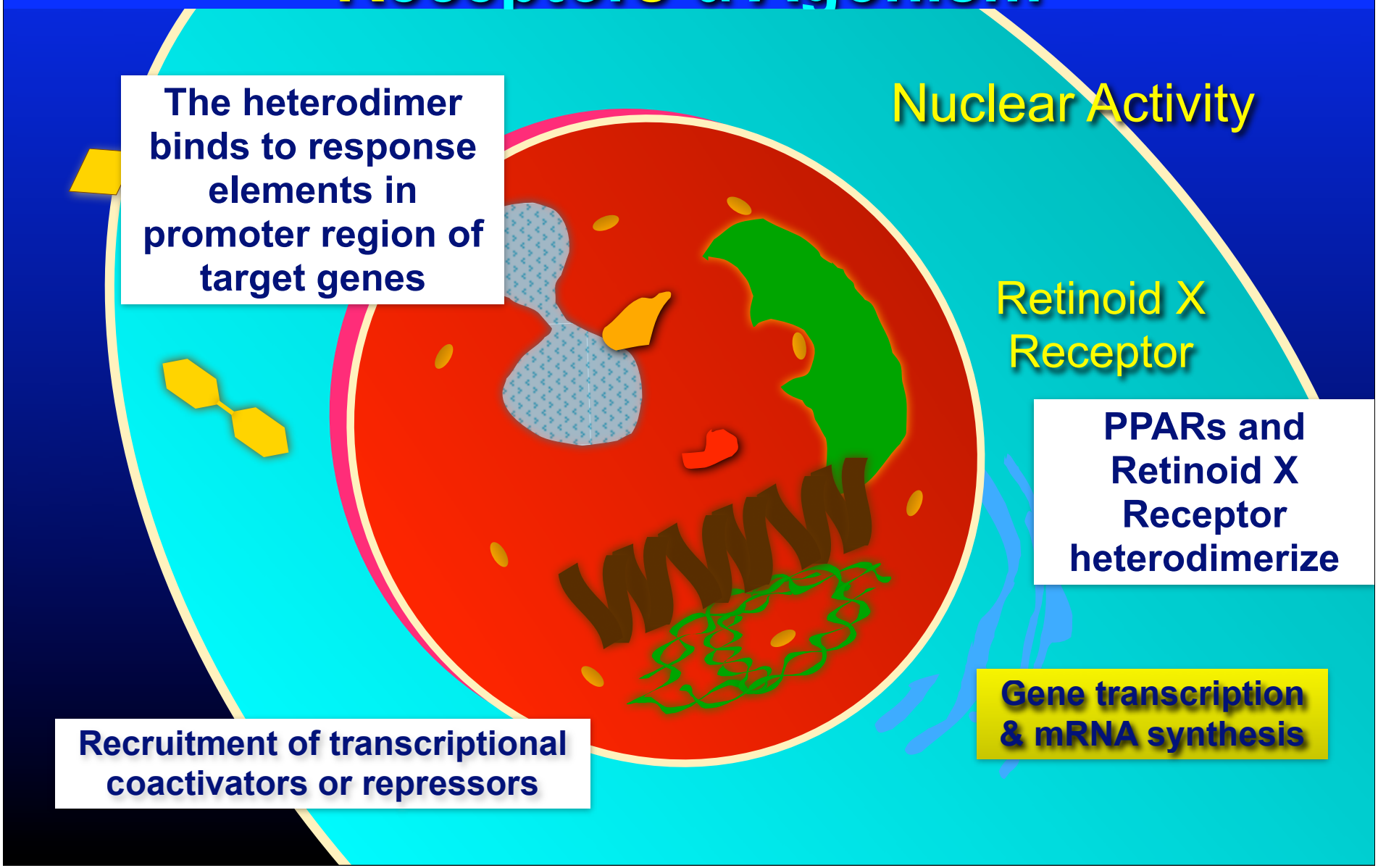
Acetylation of histone induces chromatin remodeling, a major event in activation of gene transcription.

Duplus E et al. J Biol Chem 2000;275:30749-30552

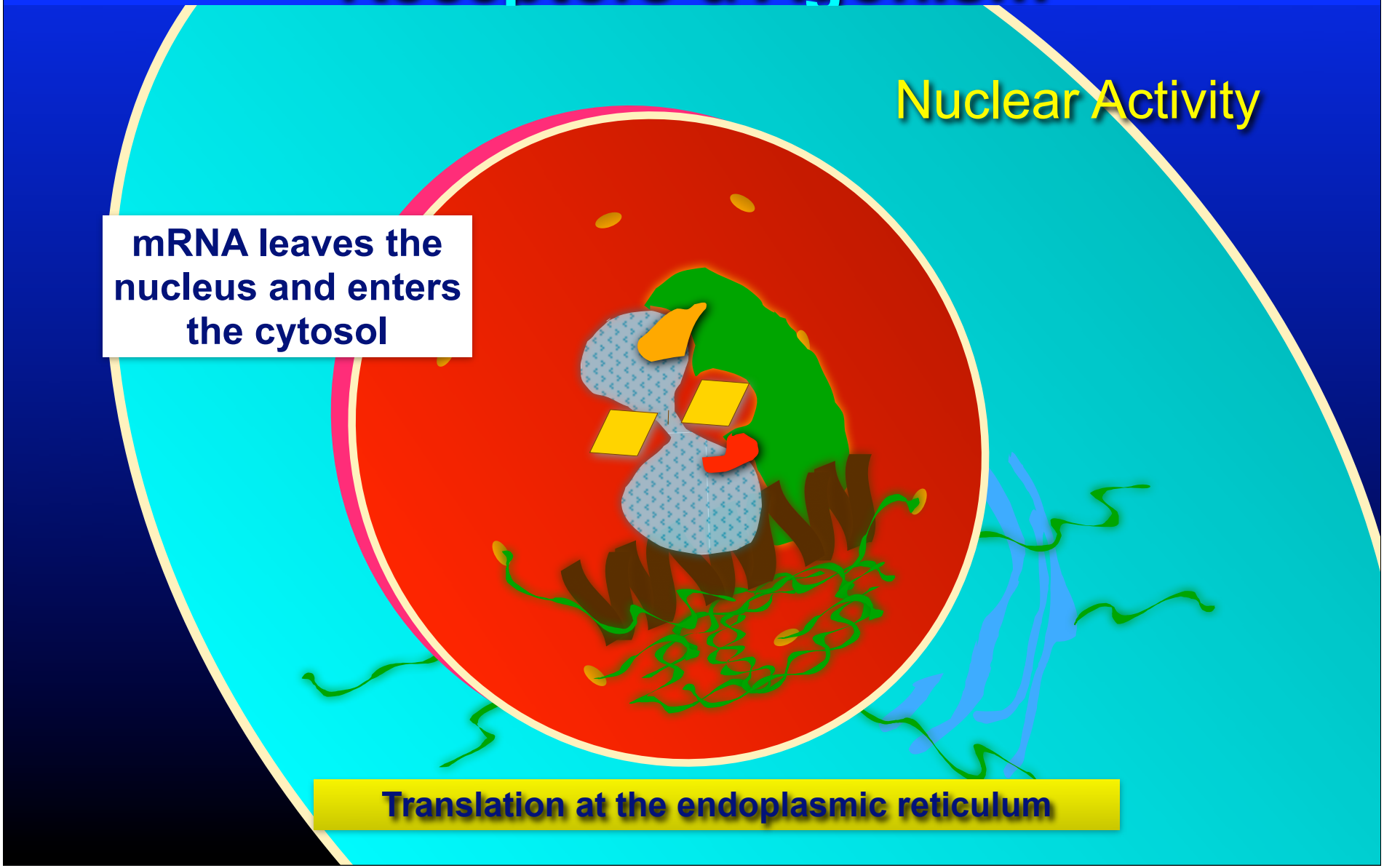
Role of Peroxisome Proliferator-Activated Receptors α (PPAR-α)

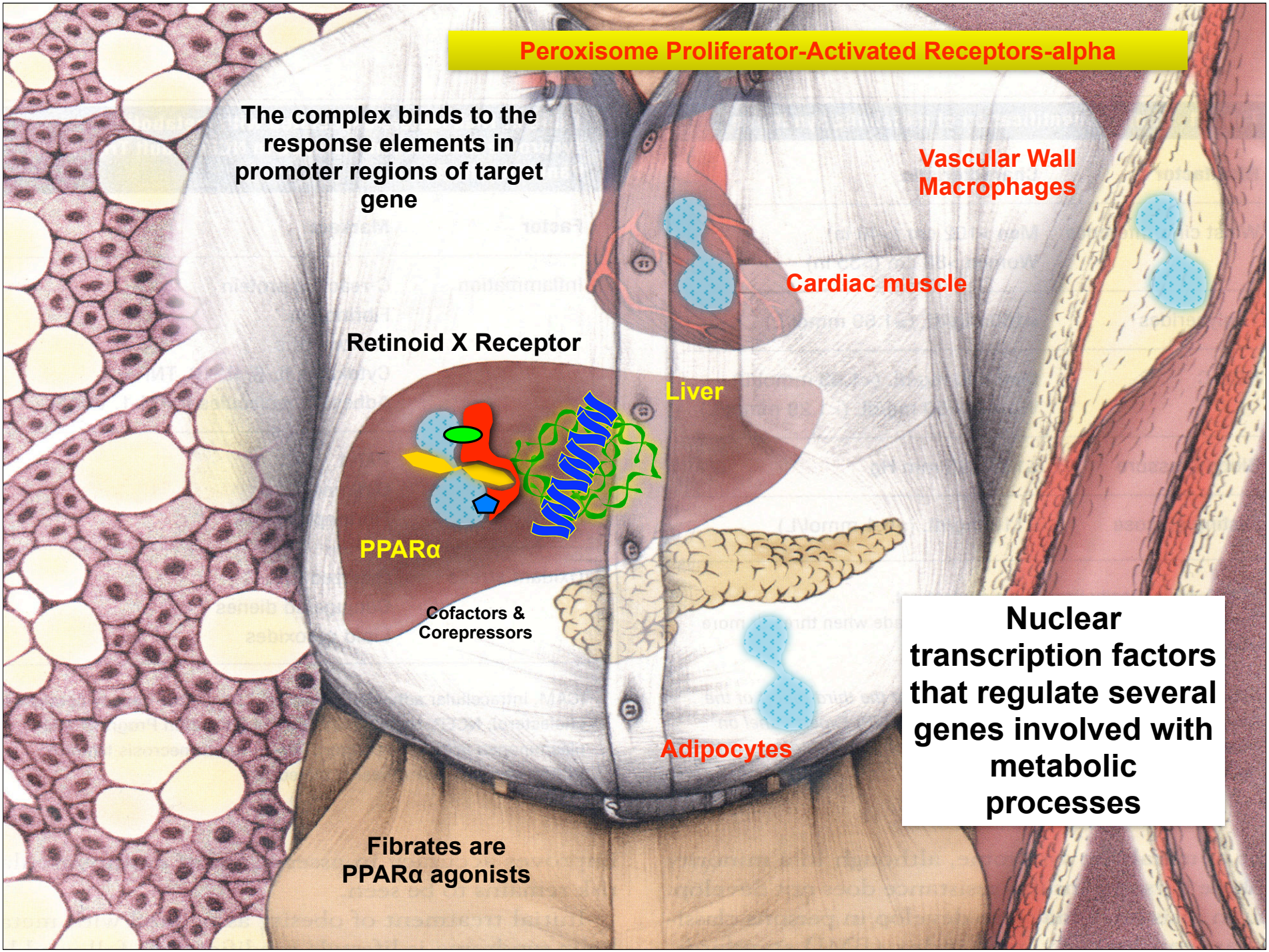


Peroxisome Proliferator-Activated Receptors α Agonism



Peroxisome Proliferator-Activated Receptors α Agonism




Peroxisome Proliferator-Activated Receptors-alpha
The complex binds to the response elements in promoter regions of target gene
Vascular Wall Macrophages
Cardiac muscle
Retinoid X Receptor
Liver
PPARα
Cofactors & Corepressors
Adipocytes
Nuclear transcription factors that regulate several genes involved with metabolic processes
Fibrates are PPARα agonists

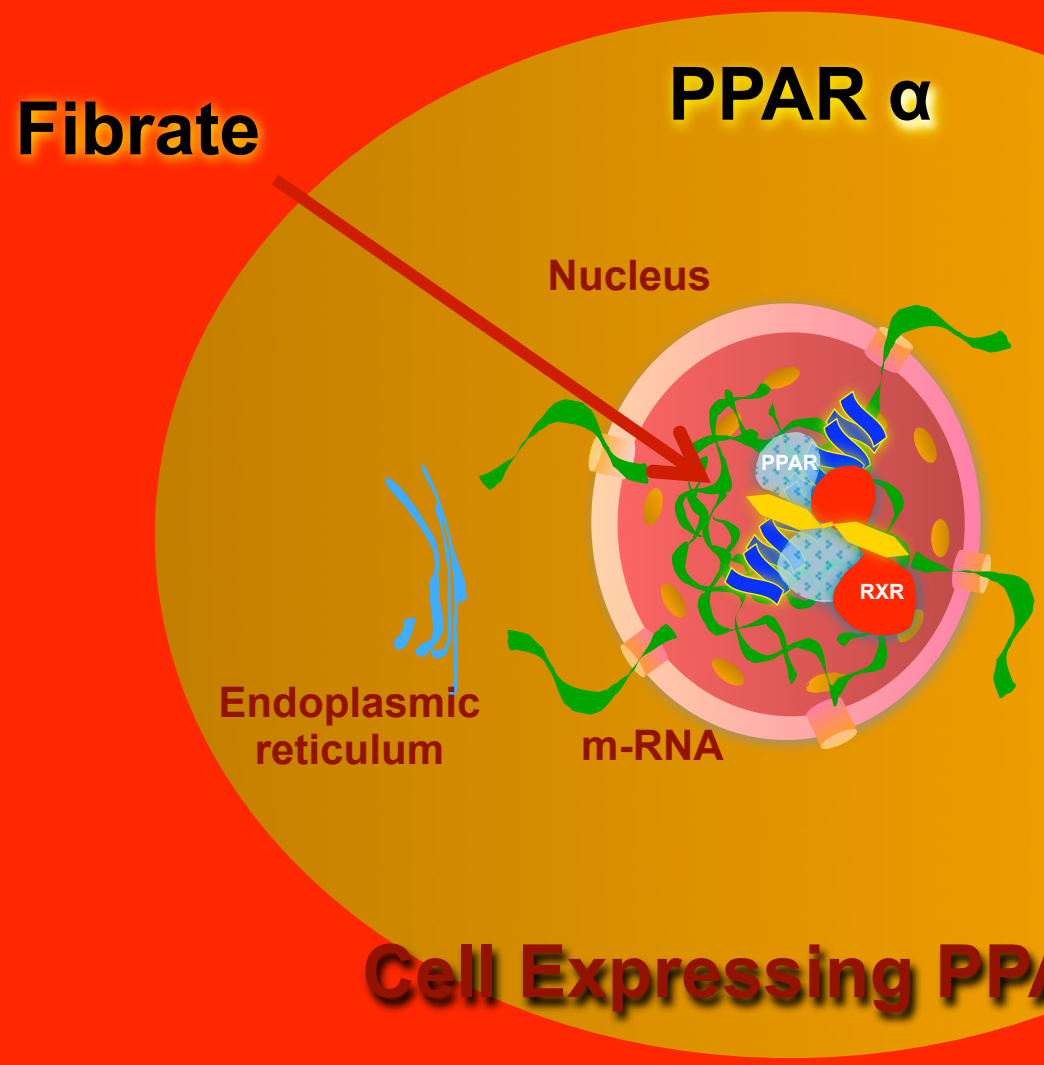
Fibrates

- Fibrates are weak agonists of peroxisomal proliferator activated receptor-alpha PPAR-α, a nuclear transcription factor which, by inducing transactivation or transrepression of multiple genes, regulates fatty acid, lipid and lipoprotein synthesis and catabolism and several aspects of vascular wall biology.
- PPAR-α also interacts (directly or via cross-talk) with other lipid-regulating genes such as liver X receptor (LXR), farnesoid X receptor (FXR), hepatic nuclear factor 4-α (HNF4-α), and angiopoietin like protein 4 (ANGPTL4).

Dayspring T & Pokrywka G Cur Athero Rep 2006, 8:356–364

Chapman JM Atherosclerosis 2003; 171: 1–13

Fibrates: PPAR-α Agonists



PPAR α is a nuclear transcription factor that regulates lipoprotein and fatty acid metabolism and other aspects of vascular biology

Fibrate Chemical Structure

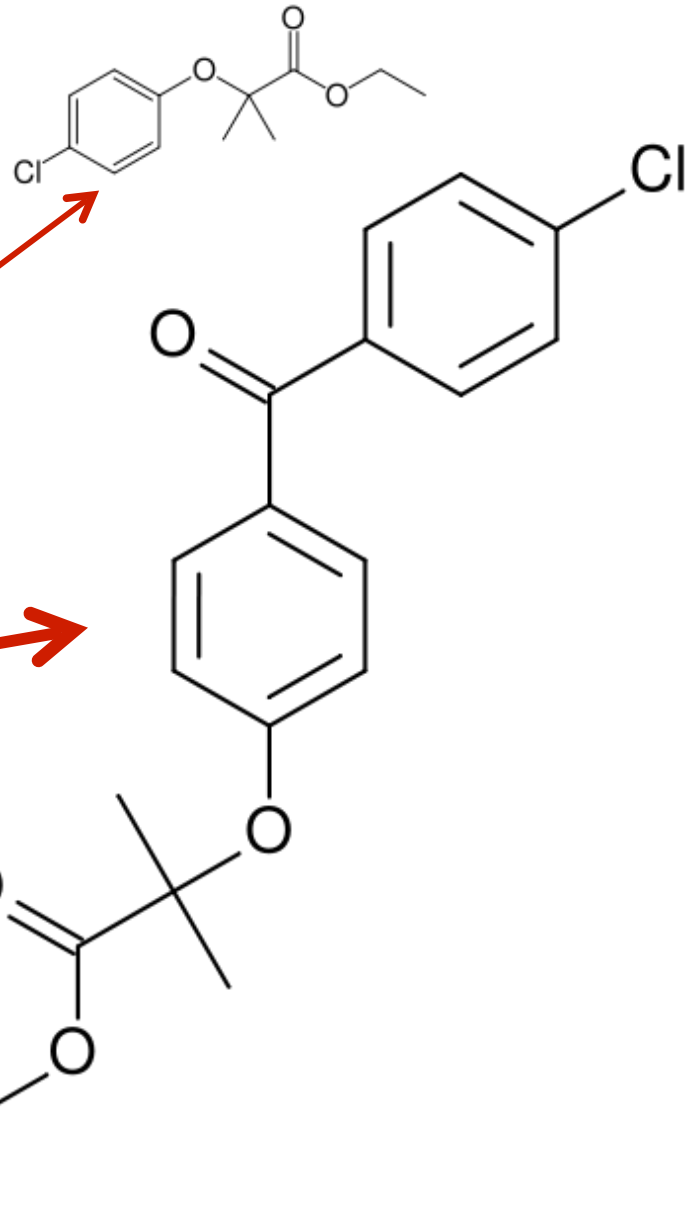
Fibrates

- Clofibrate was the first fibrate approved for use in the US in 1967
- The World Health Organization Trial was published in 1978 and it showed that despite a reduction in cholesterol it did not reduce fatal CV events, although nonfatal infarcts were reduced.
- Total mortality was greater in the clofibrate group, due to multiple causes including cholelithiasis.
- Interpretation of these negative events were clouded by failure to analyze the data according to the intention-to-treat principle.
  - A later analysis demonstrated that the apparent increase in noncardiac mortality did not persist in the clofibrate treated patients after discontinuation of the drug Lancet 1984;2:(8403):600-4

Chap 36 Goodman & Gilman Pharmacological Basis of Therapeutics McGraw Hill NY 2001

Fibrates

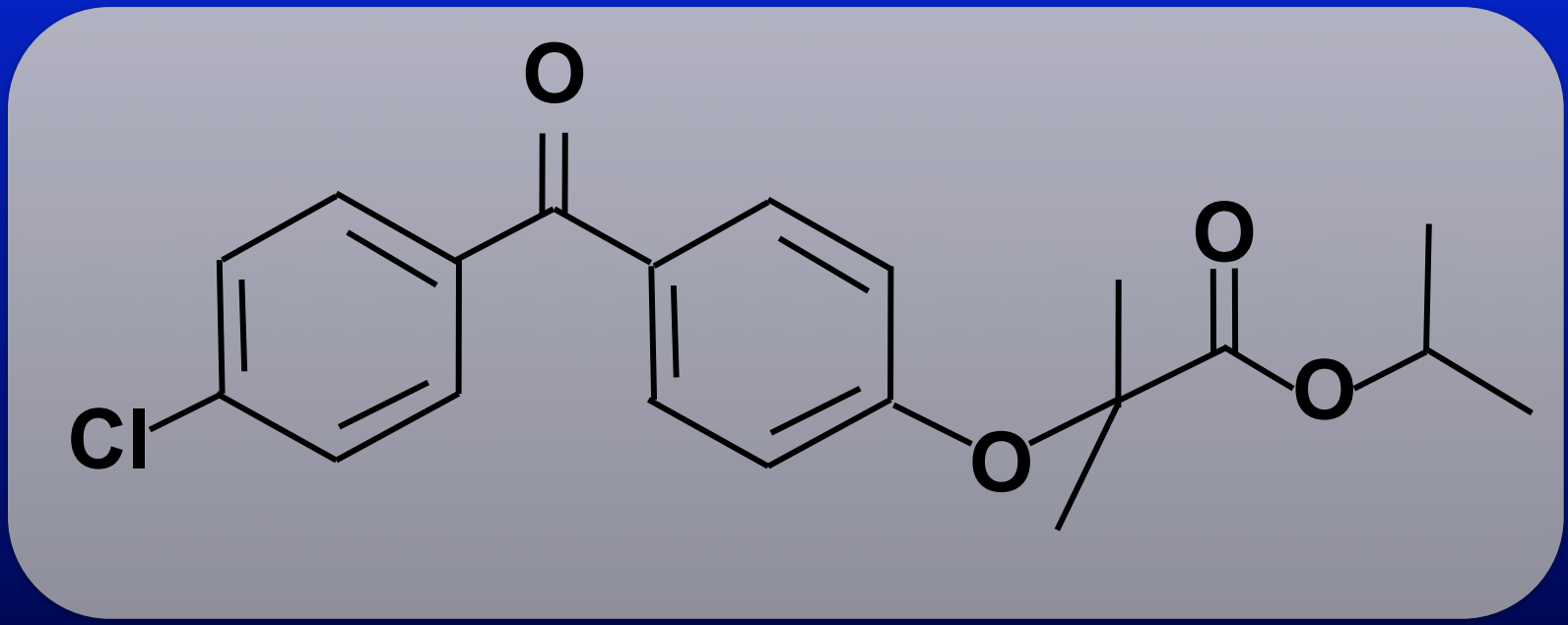
- Clofibrate , the prototype of fibric acids derivatives is the ethyl ester of p-chlorophenoxyisobutyrate.
- Gemfibrozil is a nonhalogenated phenoxypentanoic acid and is thus distinct from the halogenated fibrates
- Fibric acid analogs:
  - Fenofibrate
  - Bezafibrate
  - Ciprofibrate



Chap 36 Goodman & Gilman Pharmacological Basis of Therapeutics McGraw Hill NY 2001

Fenofibrate

1-methylethyl2-[4-(4-chlorobenzoyl) phenoxy]- 2-methyl-propanoate



Molecular Weight = 360.831 g/mol

Molecular Formula $C_{20}H_{21}ClO_4$

http://en.wikipedia.org/wiki/Fenofibrate

Fenofibrate Tablet Pharmacokinetics

- Fenofibrate is readily absorbed from the gastrointestinal tract
- Following oral administration fenofibrate is rapidly hydrolyzed to by esterases to the active metabolite fenofibric acid
- No unchanged fenofibrate is detected in the serum
- Fenofibric acid is primarily conjugated with glucuronic acid and excreted in the urine
- Neither fenofibrate nor fenofibric acid undergo oxidative metabolism by CYP450 enzymes
  - They are weak inhibitors of CYP2C19, CYP2A6 and mild-moderate inhibitors of CYP2C9 and may potentiate coumarin-type anticoagulants

Fenofibric Acid

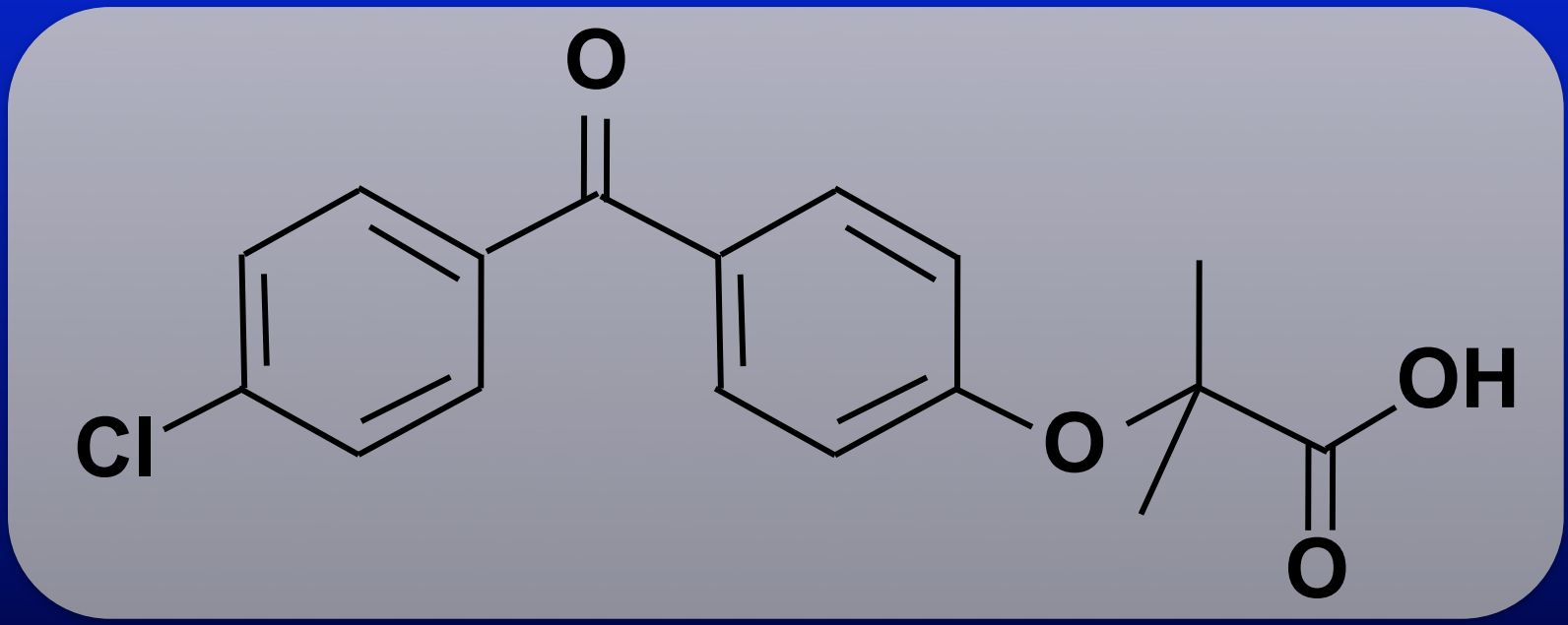
Unlike fenofibrate, fenofibric acid contains a carboxylic acid moiety instead of an ester moiety.

This polar moiety plays an important role in the formation of a rare acid-to-ketone hydrogen-bond-type packing interaction. The lack of an isopropyl group in fenofibric acid aligns the carboxyl group on the same side as the ketone carbonyl group; this conformation may play an important role in discrimination between the acid and the fenofibrate molecule in molecular recognition.

http://journals.iucr.org/c/issues/2005/02/00/sq1185/sq1185bdy.html

Fenofibric Acid

2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic acid; 2-[4'-(p-Chlorobenzoyl)phenoxy]-2-methylpropionic acid



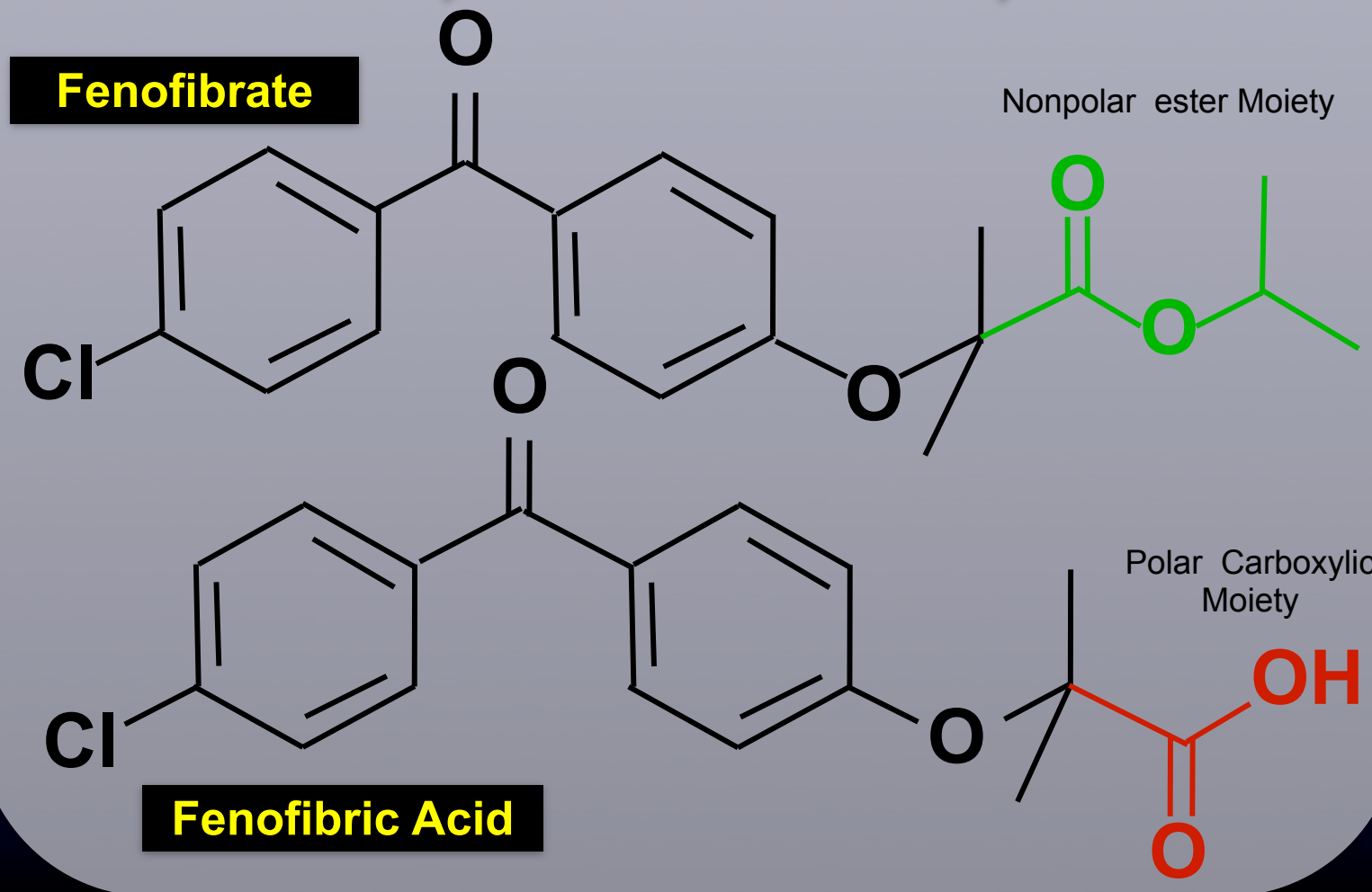
Molecular Weight = 318.76

Molecular Formula $C_{17}H_{15}ClO_4$

http://www.chemblink.com/products/42017-89-0.htm

Fenofibrate vs Fenofibric Acid

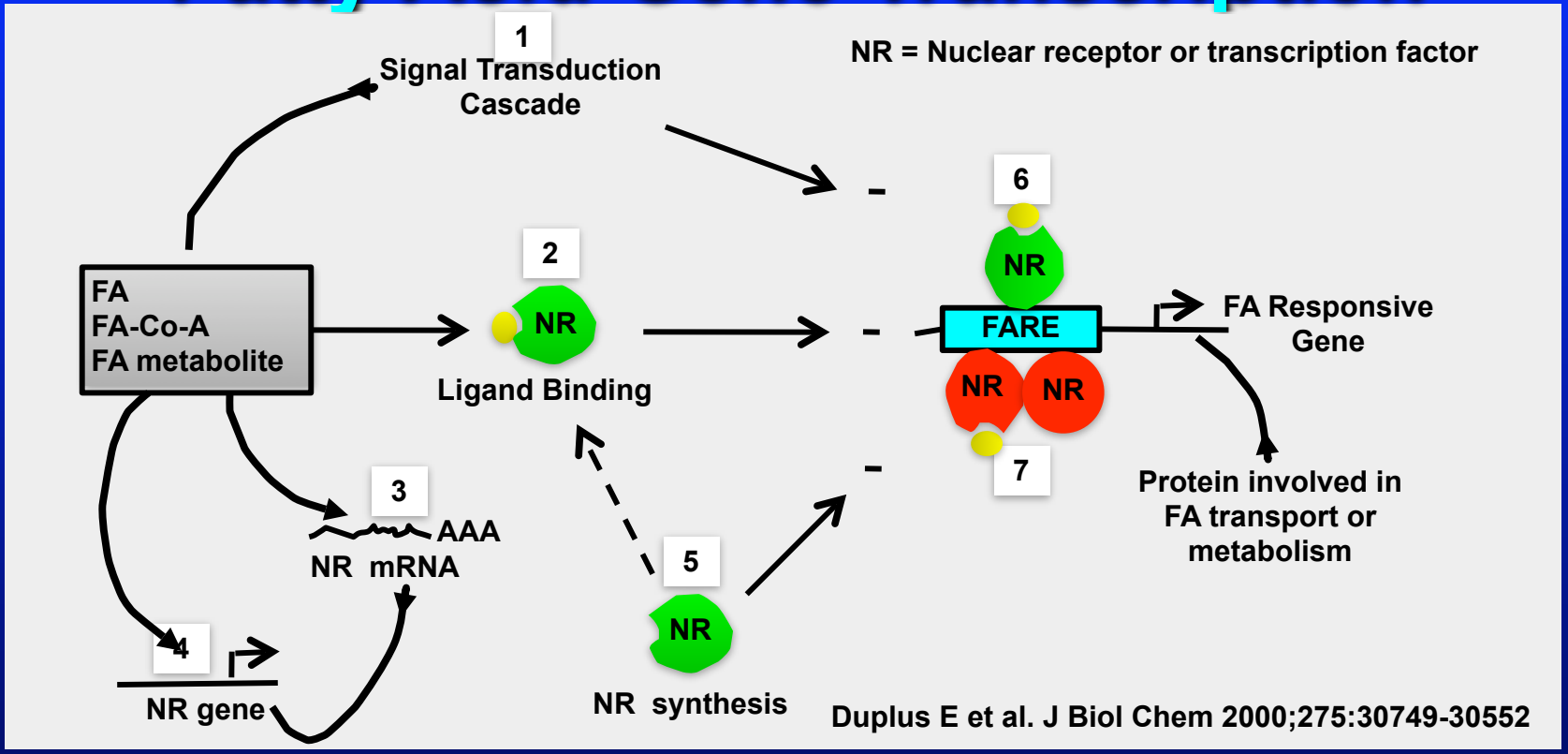
Unlike fenofibrate fenofibric acid contains a carboxylic acid moiety instead of an ester moiety.



Fibrate Effect on Lipids and Lipoproteins

Triglycerides

Fatty Acid Gene Transcription



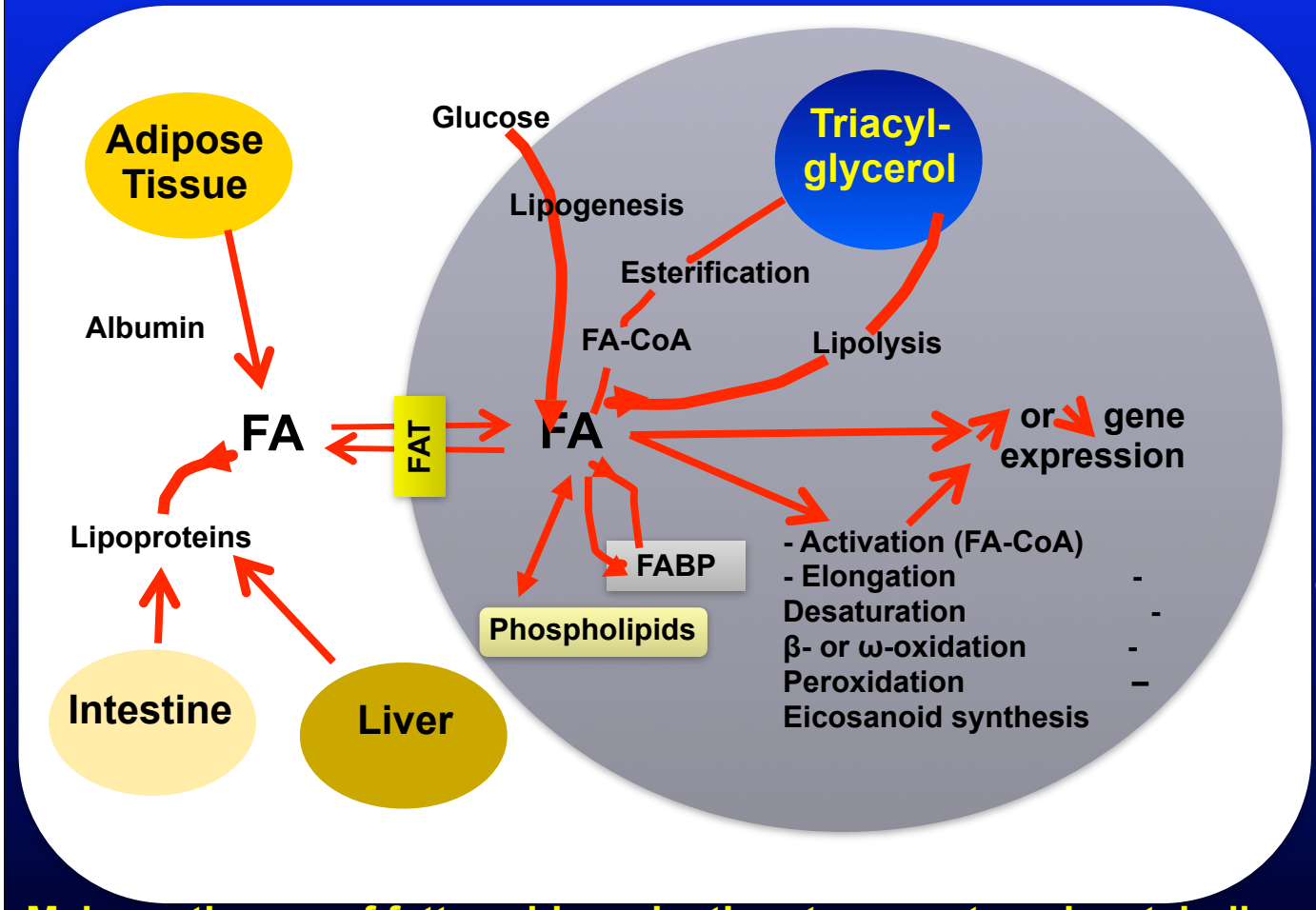
The FA per se, FA-CoA, or FA metabolite modulate (±) transcription of a responsive gene, encoding a protein involved in FA transport or metabolism, through various non-mutually selective potential mechanisms. Step 1, a signal transduction cascade is initiated to induce a covalent modification of a NR, thereby modifying its transcriptional potency. Step 2, the FA itself or its derivative acts as a ligand for a NR, which then can bind DNA at a FA response element (FARE) and activate or repress transcription. Steps 3, 4, and 5, FA can act indirectly via alteration in either NR mRNA stability (Step 3) or gene transcription (Step 4), resulting in variations of de novo NR synthesis (Step 5) with an impact on the transcription rate of genes encoding proteins involved in FA transport or metabolism. On binding to the cognate response element, NR acts either as a monomer (Step 6), a homodimer, or a heterodimer with NR, a different NR (Step 7).

Fibrate Mechanisms of Action

- De novo fatty acid synthesis is also inhibited with fenofibrate, through reductions in acetyl-CoA carboxylase and fatty acid synthase activity;
- This also reduces the availability of fatty acids for TG synthesis.
- Fenofibrate also promotes the β-oxidation of fatty acids, thus reducing the availability of free fatty acids for TG synthesis
- ApoB and VLDL production and secretion is also reduced with fenofibrate

Gillian M. Keating and Katherine F. Croom. Drugs 2007; 67 (1): 121-153

Fatty Acid Pathways



Major pathways of fatty acid production, transport, and metabolism.

FA are released by adipose tissue after lipolysis or by lipoproteins arising either directly from the intestine after a lipid-rich meal or from the liver. FAs circulate in the plasma loosely bound to albumin (ALB) and cross plasma membrane with the help of a FAT.

In lipogenic cells like hepatocytes and adipocytes, they can be synthesized from glucose (lipogenesis). Inside the cell they bind to a cell-specific cytosolic FABP and can be exchanged with FAs of membrane phospholipids (PL). Mainly in liver and adipose tissue they can be activated into fatty acyl-CoA(FA-CoA) and esterified to glycerol-3-phosphate to synthesize triacylglycerol. In many cell types,

FAs can be elongated and desaturated by specific enzymes(elongases and desaturases), β-oxidized in mitochondria or peroxisomes, ω-oxidized in microsomes, peroxidized, or participate in eicosanoid (prostaglandins, leukotrienes, thromboxanes) synthesis.

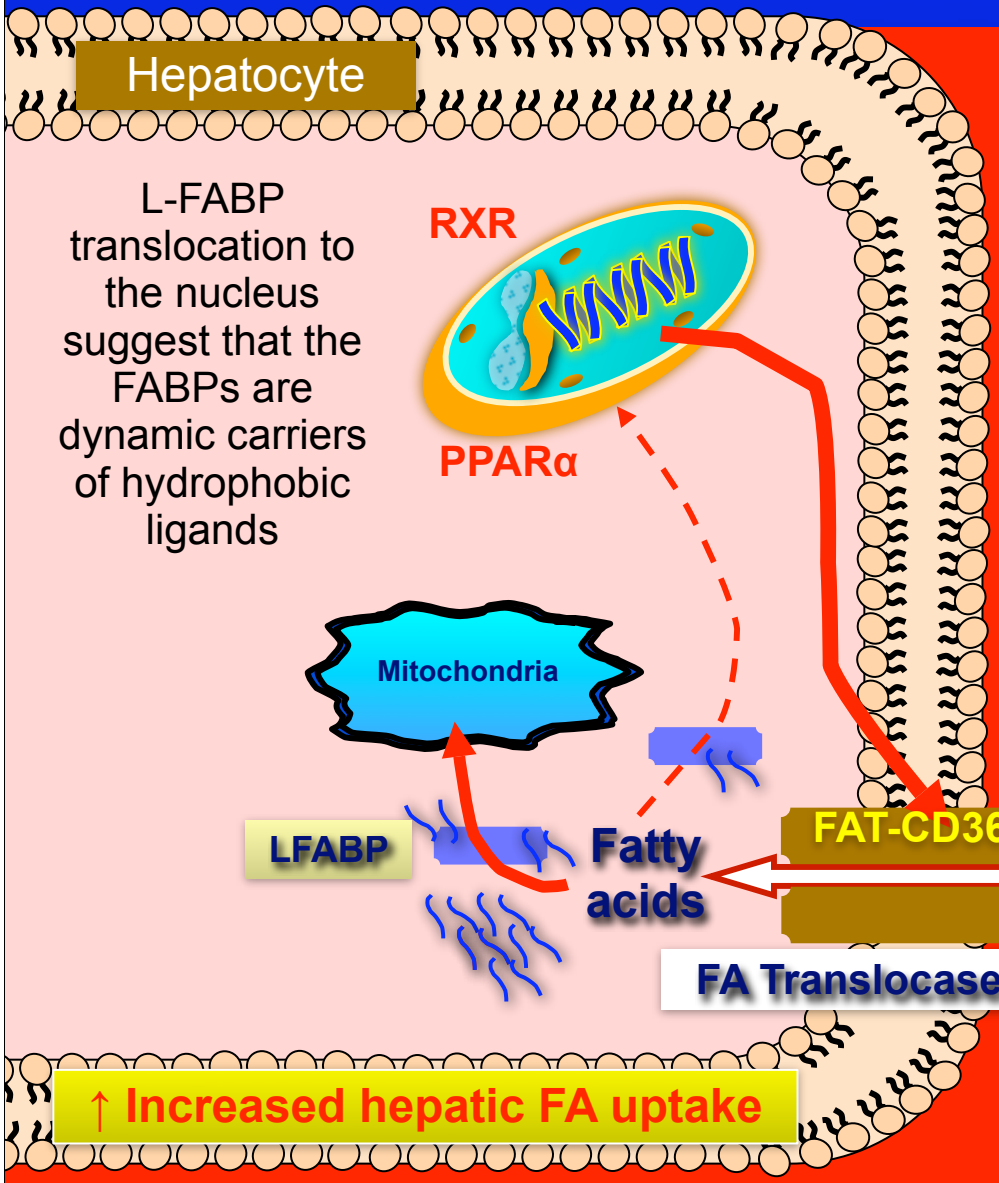
Duplus E et al. J Biol Chem 2000;275:30749-30552

Fatty Acid Transport Proteins

- In the cell, a signaling molecule is the free FA (not bound to albumin), which is transported in and out cells with the help of a membrane protein, the FA transporter (FAT).
- Six potential FAT candidates have been cloned and characterized.
  - FA translocase (FAT-CD36),
  - FA transport protein,
  - Mitochondrial aspartate aminotransferase,
  - Caveolin,
  - Adipose differentiation-related protein,
  - FA-binding protein (FABP, a cytosolic protein that can bind to membranes)

Duplus E et al. J Biol Chem 2000;275:30749-30552

Fibrates and Liver Fatty Acid Binding Proteins (LFABP)



The LFABP promoter contains a peroxisome proliferator response element which helps deliver ligands to cellular enzymes or membranes. L-FABP is involved in communicating the state of fatty acid metabolism from the cytosol to the nucleus through an interaction with lipid mediators that are involved in nuclear signal transduction.

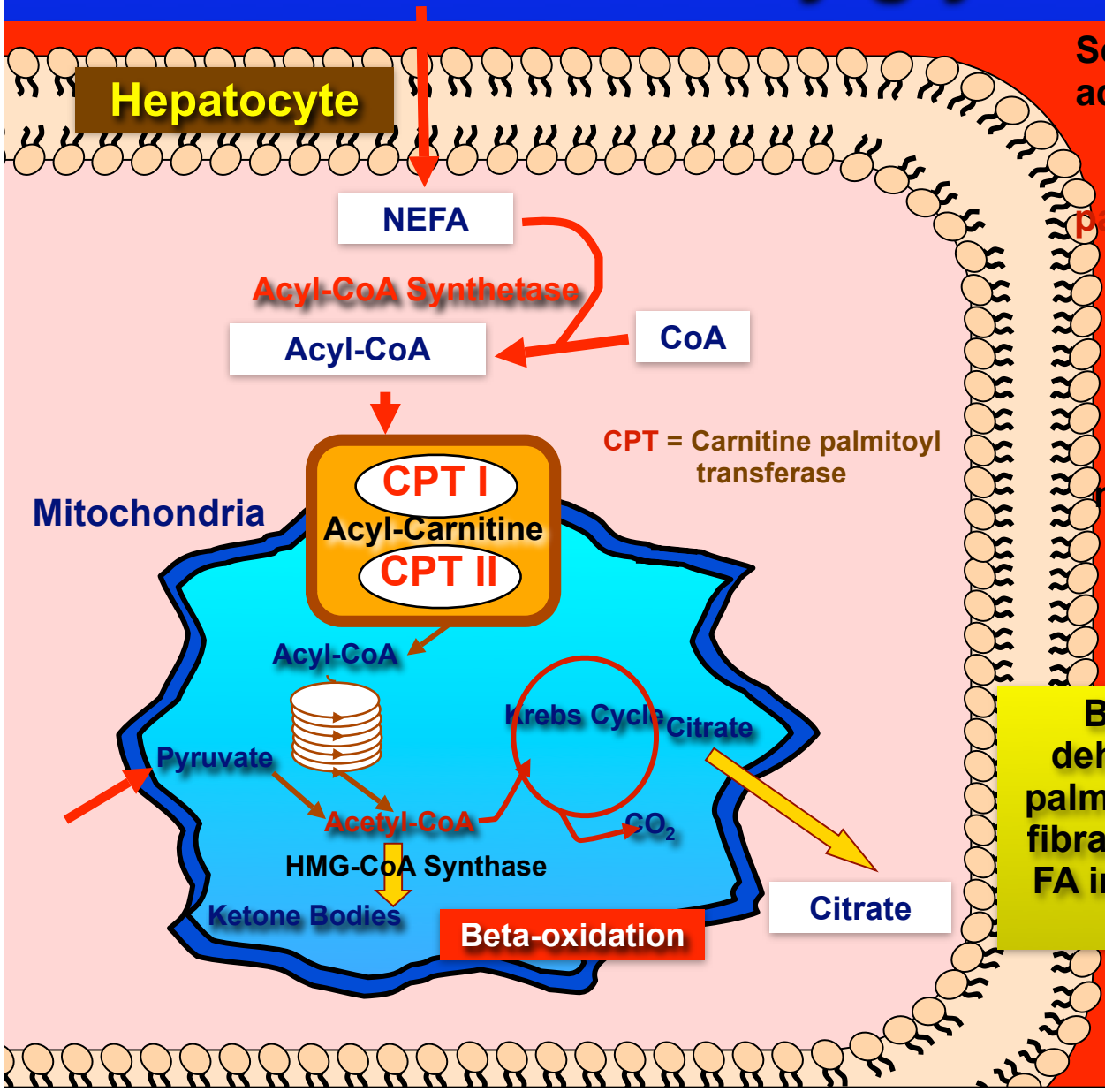
The transcription rate of the L-FABP gene is tightly regulated and induced by both fibrate hypolipidemic drugs and Long Chain FA through a peroxisome proliferator-activated receptor (PPAR)-responsive element located in the proximal part of the promoter. Several lines of evidence show that L-FABP participates in the cellular uptake and trafficking of FA.

Landrier JF et al. JBC 2004;279:45512-45518

Duplus E et al. J Biol Chem 2000;275:30749-30552

Lawrence JW et al. J. Lipid Res. 2000.41:1390–1401

Fibrates and Triacylglycerol Synthesis



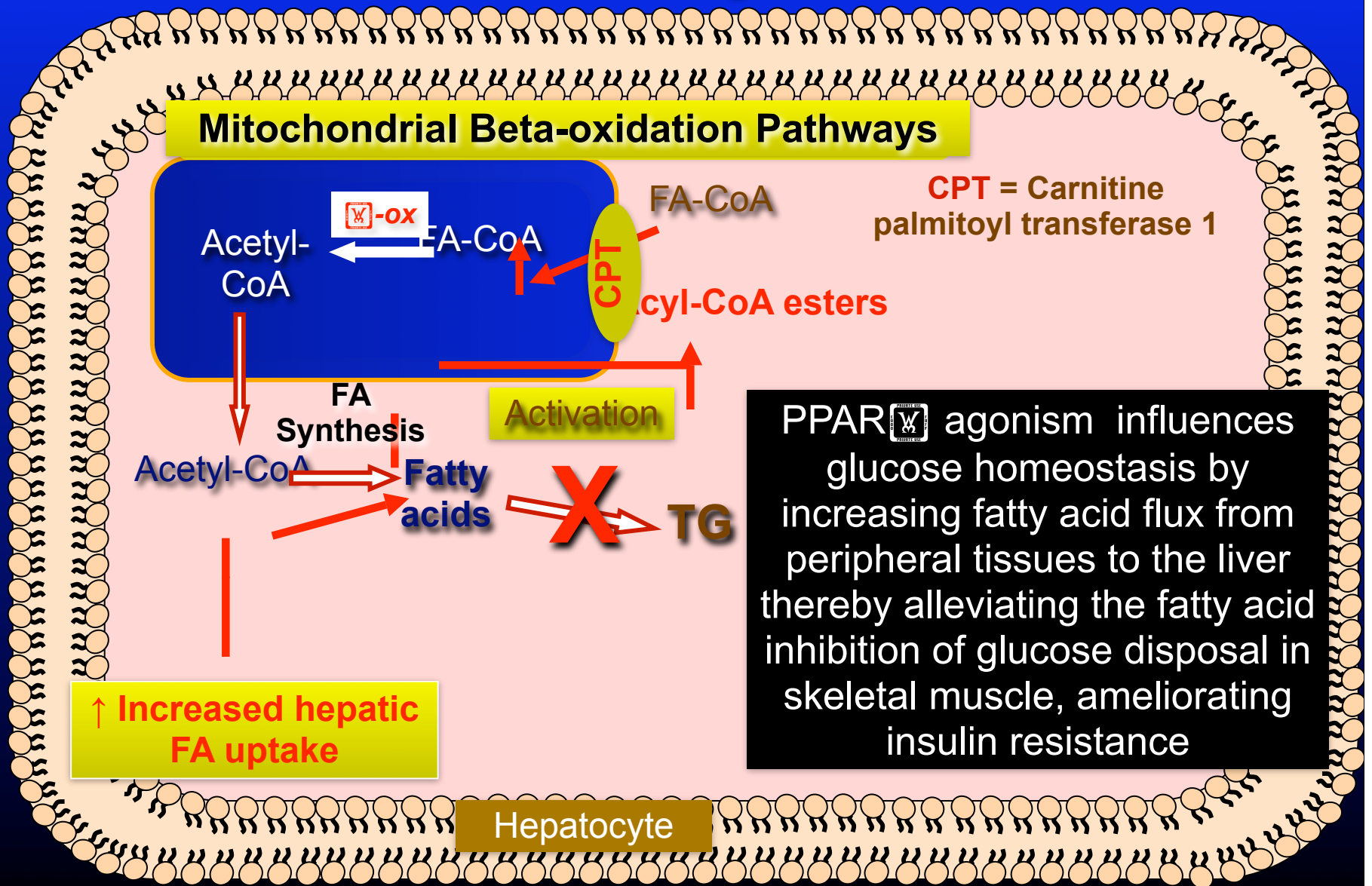
Schematic representation of fatty acid metabolism in the liver: fatty acid oxidation: acyl-CoA synthetase, and carnitine palmitoyltransferase I [CPT I]) are shown.

Non-esterified fatty acids (NEFAs) are substrates for triglyceride synthesis and they undergo beta-oxidation in the mitochondria to form acetyl-CoA which enters the Krebs cycle and converts to citrate, a precursor of TG.

By inducing both acyl CoA dehydrogenases and carnitine palmitoyltransferase I (CPT I), the fibrates facilitate translocation of FA into mitochondria where they undergo beta-oxidation.

Pegorier JP et al. J Nutr 2004;134(9):2444S-9S
Kesting GM et al. Drugs 2007;67:121-153

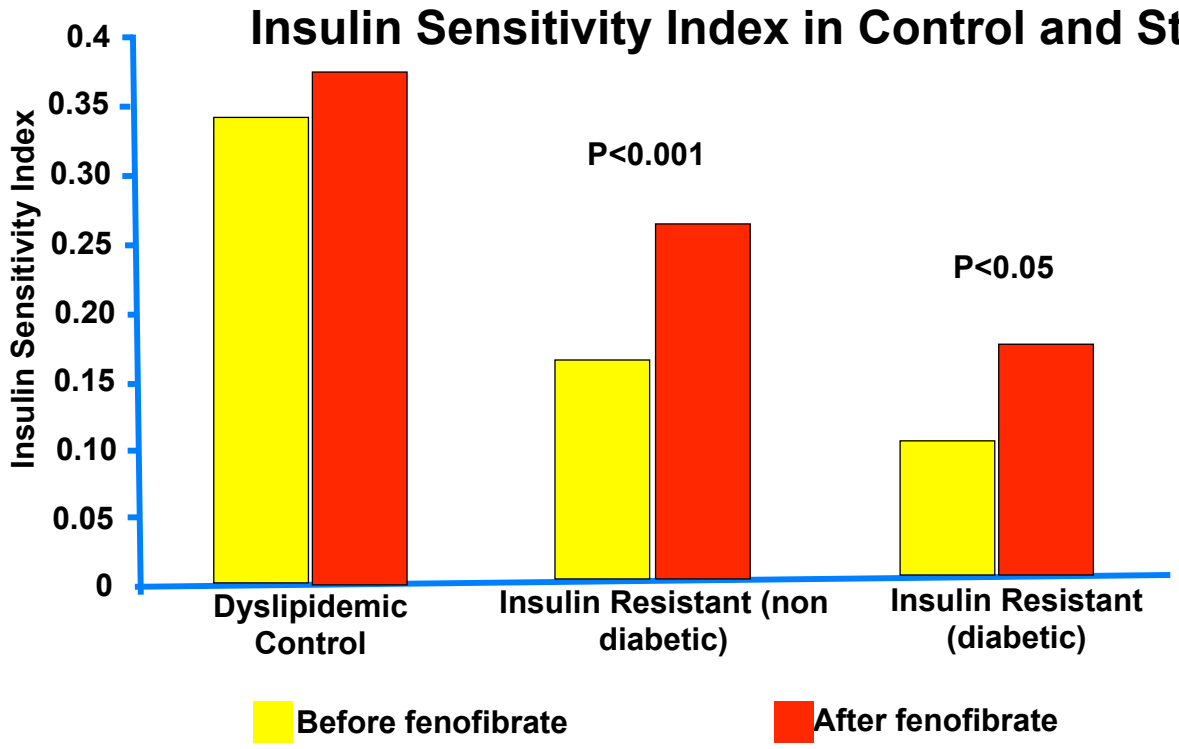
PPAR α Increases Fatty Acid Catabolism



PPAR agonism influences glucose homeostasis by increasing fatty acid flux from peripheral tissues to the liver thereby alleviating the fatty acid inhibition of glucose disposal in skeletal muscle, ameliorating insulin resistance

Pineda, T. et al. Curr Opin Lipidol 1999;10:151-159

Effects of Micronized Fenofibrate on Insulin Resistance in Patients with the Metabolic Syndrome

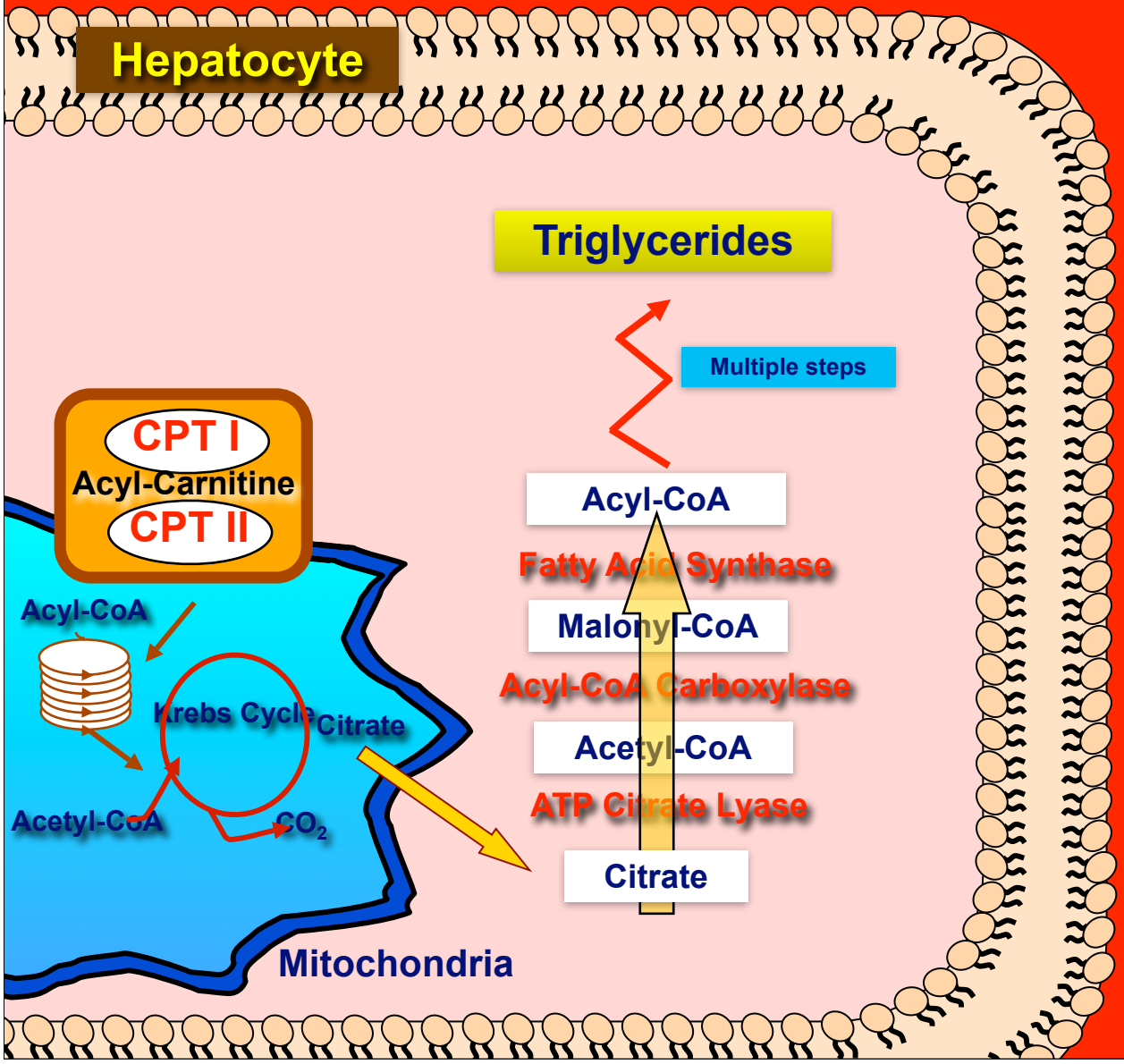


Micronized fenofibrate is effective in the therapy of lipid-lipoprotein abnormalities associated with the metabolic syndrome.

This effectiveness results not only from its influence on the lipid profile but also from a reduction in insulin resistance

Wysocki, J et al. Int Jour Clin Pharm & Ther 2004;42:212-217

Fibrates and Triacylglycerol Synthesis



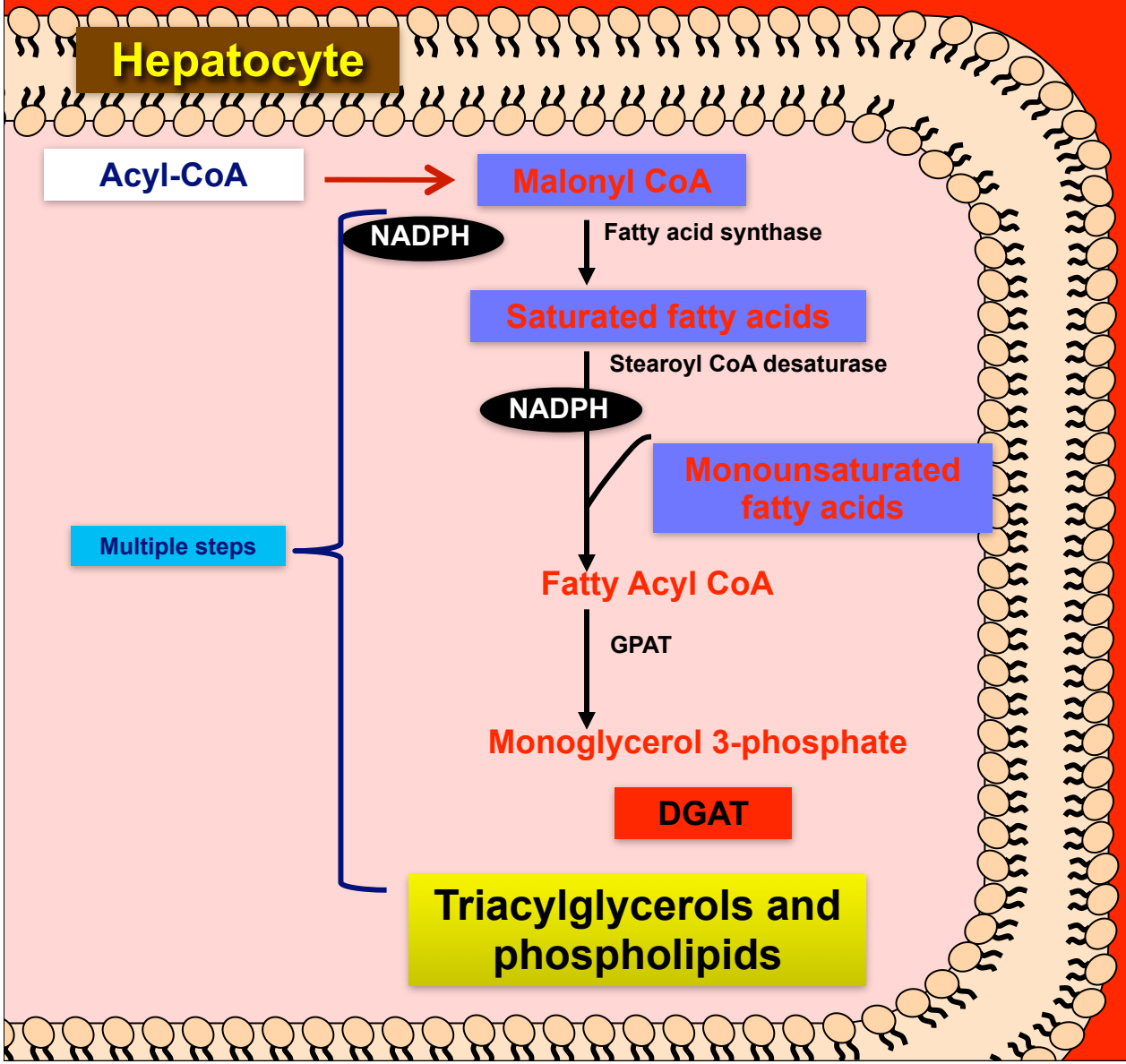
Schematic representation citrate, produced by NEFA conversion via the Krebs cycle, initiating the triglyceride synthesis pathways.

Fenofibrate inhibits de novo fatty acid synthesis through reductions in acetyl-CoA carboxylase and fatty acid synthase activity;

This also reduces the availability of fatty acids for TG synthesis.

Pegorier JP et al. J Nutr 2004;134(9):2444S-9S
Kesting GM et al. Drugs 2007;67:121-153

Fibrates and Triacylglycerol Synthesis



Schematic representation of the multiple steps between acyl-CoA to TG synthesis

Fenofibrate ester decreases de novo FA synthesis by repressing the expression of SREBP1 and fatty acid synthase secondary to LXR antagonism.

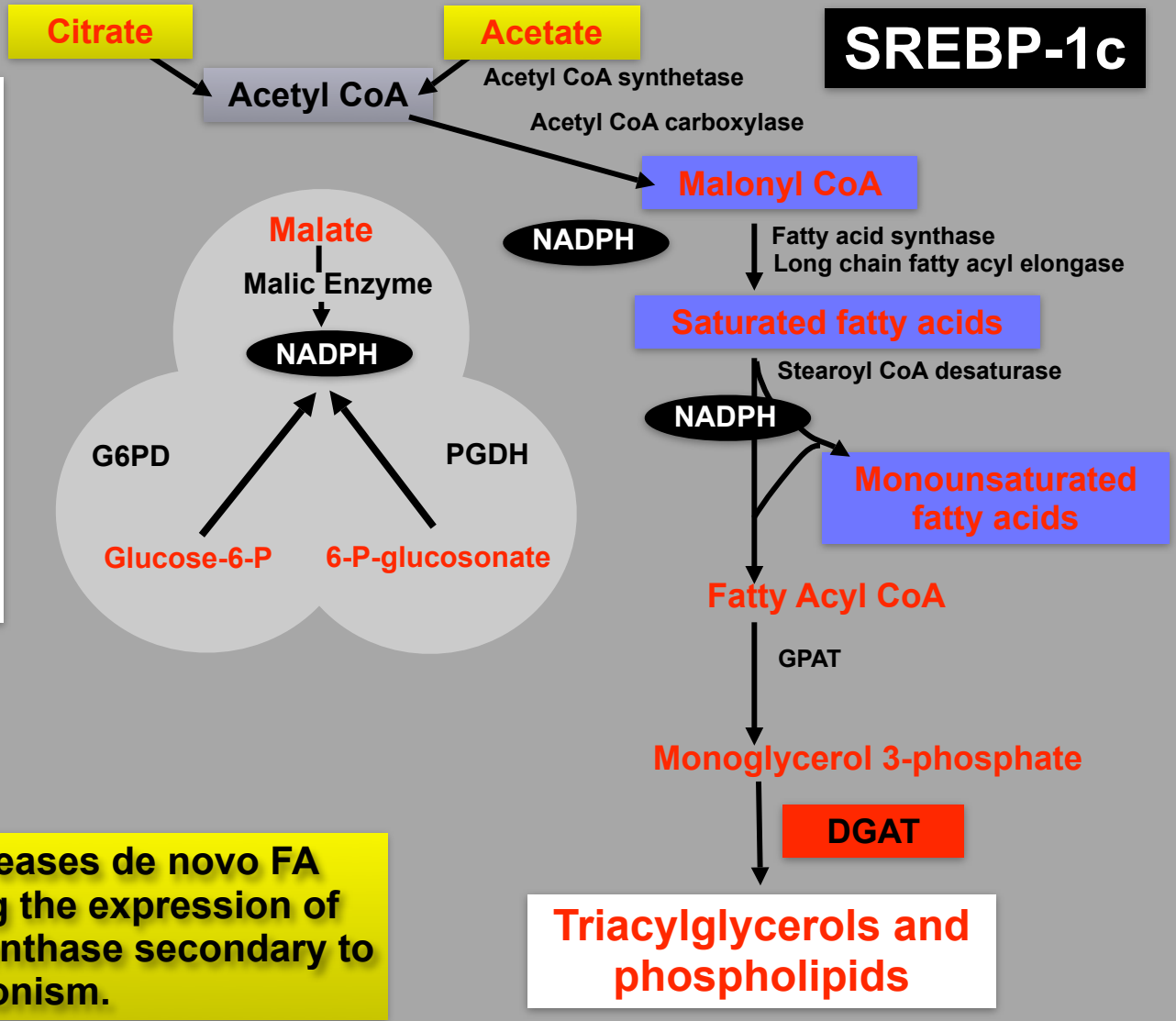
Fibrates also noncompetitively inhibit diacylglycerol acyl transferase 2 (DGAT2),

Pegorier JP et al. J Nutr 2004;134(9):2444S-9S
Kesting GM et al. Drugs 2007;67:121-153

Nuclear Transcription Factors & Triglycerides

Liver X Receptor beta (LXR-β) influences the Sterol Regulatory Element Binding Protein (SREPB 1c)

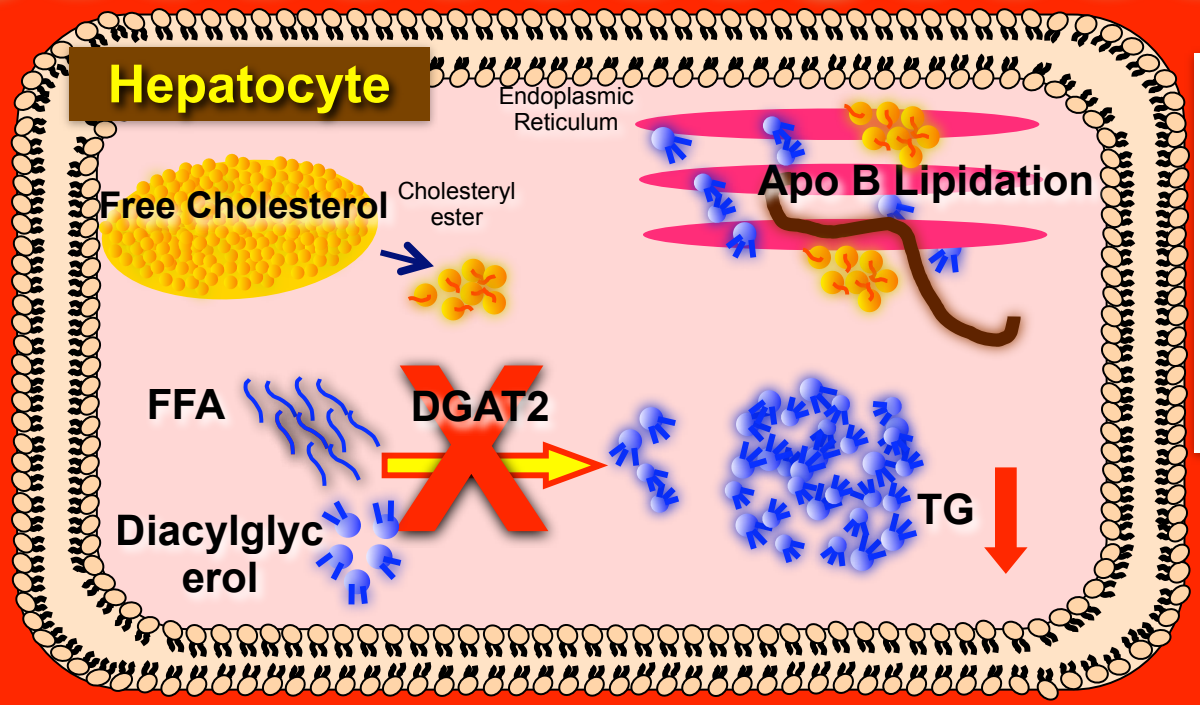
SREBP-1C stimulates the lipogenic enzyme genes which influence triglyceride & phospholipid synthesis



Fenofibrate ester decreases de novo FA synthesis by repressing the expression of SREBP1 and fatty acid synthase secondary to LXR antagonism.

Adapted from Horton, Goldstein & Brown. J. Clin. Invest. 109:1125–1131 (2002).

Fibrates and Triglyceride Synthesis



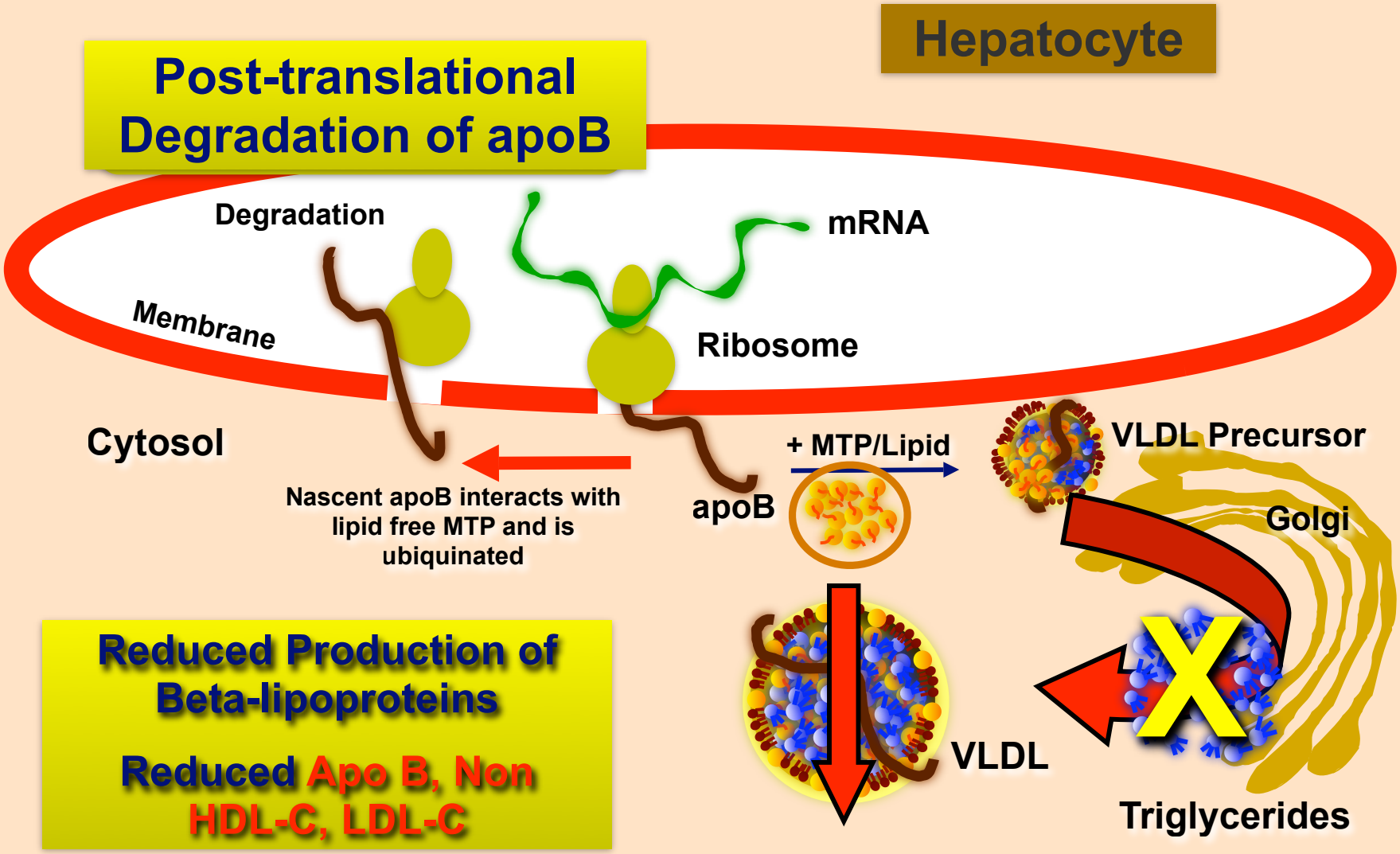
Diacylglycerol 2 acyltransferase (DGAT2) is a microsomal enzyme that plays a role in the hepatic assembly of de novo synthesized fatty acid into TG

DGAT2 catalyzes the terminal and only committed step in cellular TG synthesis by using diacylglycerol and fatty acyl-CoA as its substrates

Gemfibrozil, a fibrate non-competitively and directly inhibits DGAT2 reducing TG synthesis and subsequently apoB lipidation

Zhu D, et al Atherosclerosis 2002, 164:221–228.

Fibrates Decrease VLDL Synthesis



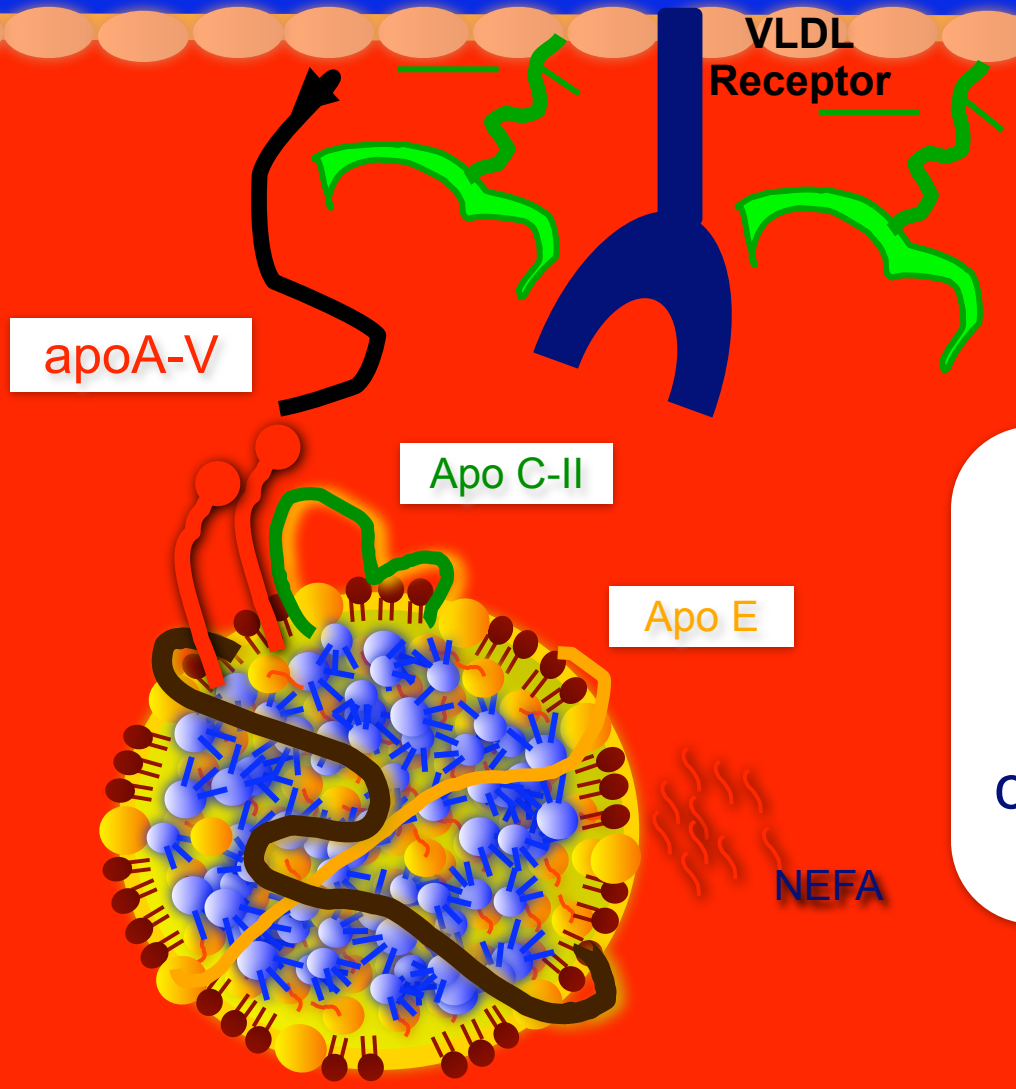
Zhu D, et al Atherosclerosis 2002, 164:221–228.

Fibrate Mechanisms of Action

- Fibrates reduce TG by the combined actions of suppressing
  - FA synthesis,
  - Increasing FA oxidation,
  - Inhibiting the esterification of diacylglycerols
- Fibrates increase post-translational degradation of apoB and the secretion of VLDLs.

Toth P, Dayspring T & Pokrywka G Cur Atheroscler Reports in Press

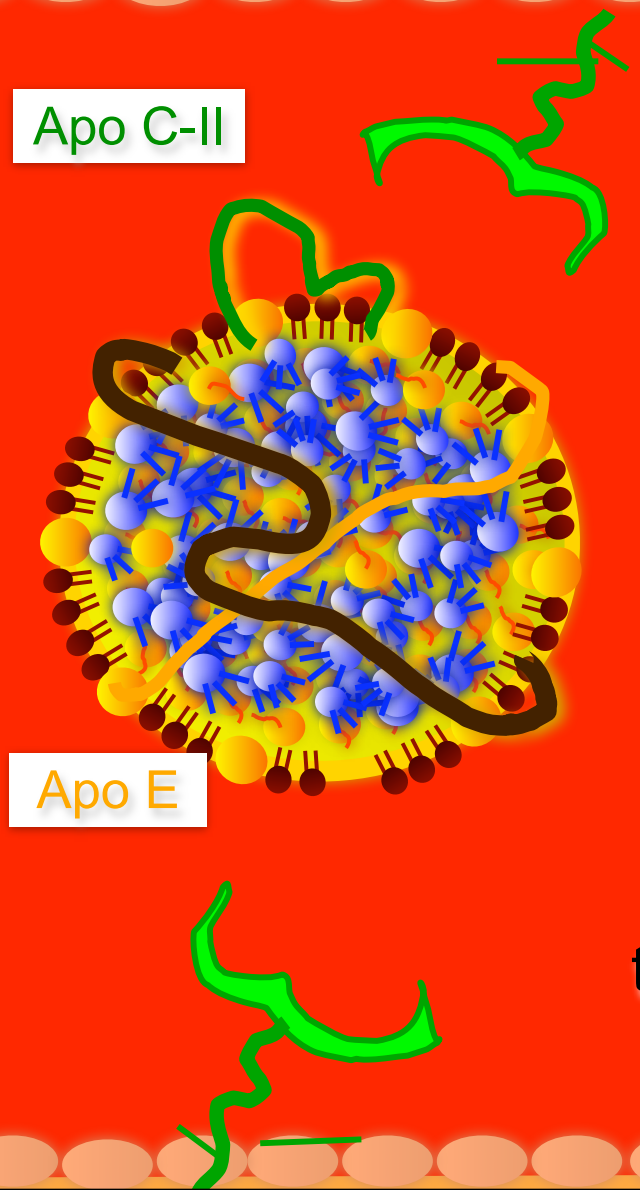
Fibrates Increase ApoA-V Production



Fibrates increase apoA-V production enhancing the anchoring of TG-rich lipoproteins like VLDL and chylomicrons at sites of LPL expression

Schultze AE et al. J Lipid Res 2005;46:1591-95

Fenofibrate Indices LPL Expression



Lipoprotein Lipase (LPL)

PPARα induction of hepatic LPL synthesis

Enhances lipolysis of TG-rich lipoproteins decreasing their half life

ApoC-II binds to LPL and then TG hydrolysis occurs

Schoonjans K, et al. J LipidRes 1996, 37:907–925.

VLDL Lipolysis: PPARα Effect

Apo C-III blocks LPL from the ligand Apo CII

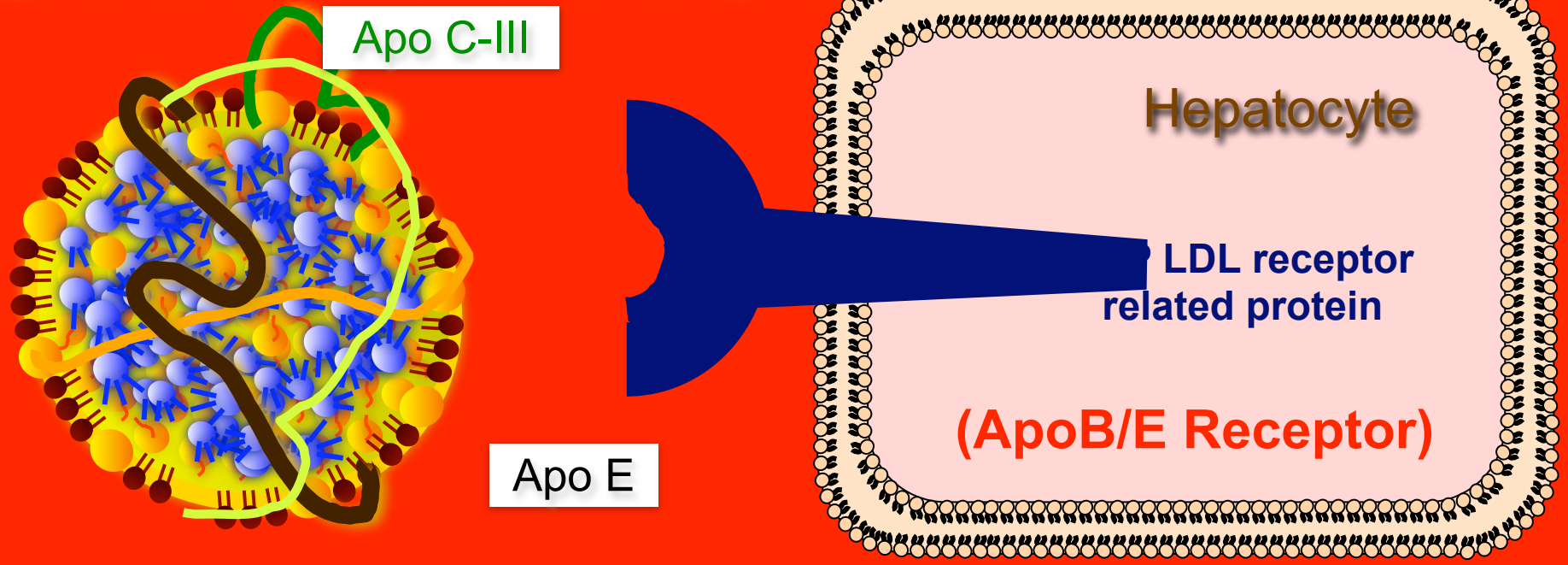
Fibrate PPARα agonism reduces Apo C-III production

With Apo C-III absent, LPL can bind with Apo CII

Hydrolysis of TG occurs

Fruchart JC, et al. Cell Physiol Biochem 1999;9:139–149

Hepatocyte Removal of VLDL
PPARα Agonistic Effect on ApoC-III



- LDL receptor related (LRP) protein expressed
- Without Apo C-III (fenofibrate↓hepatic production)
- Apo E, the ligand for LRP is exposed

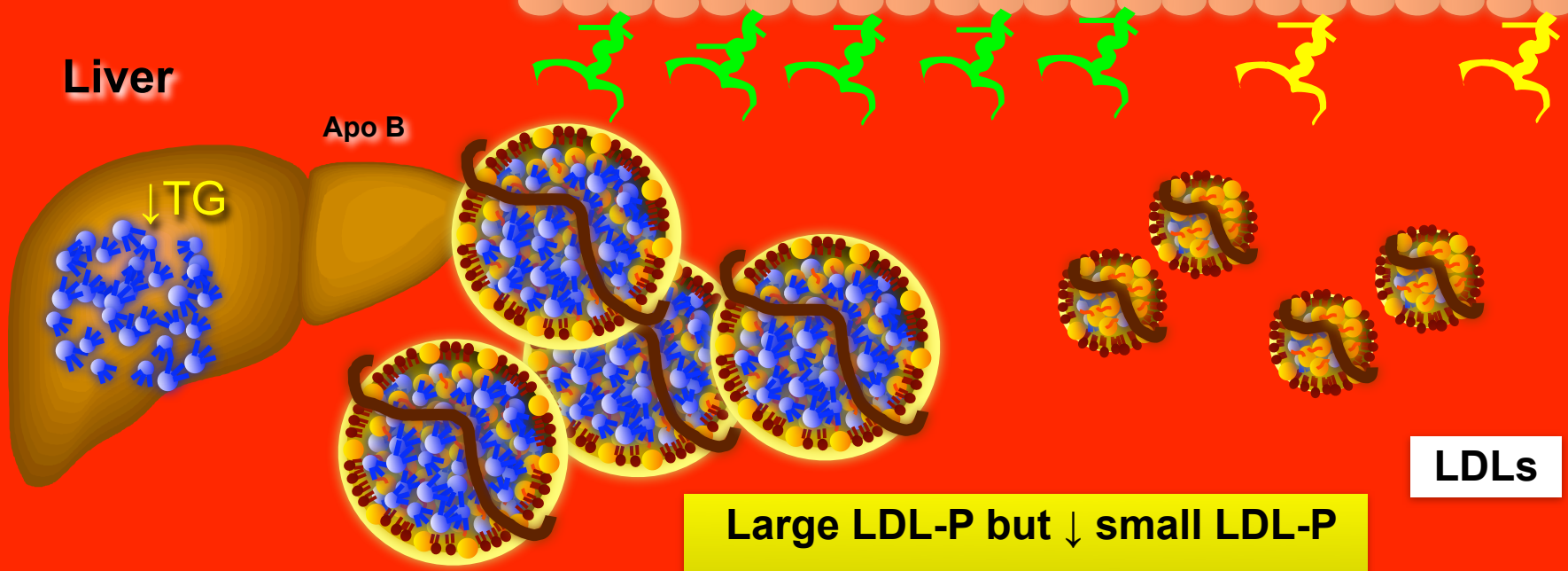
Fibrate Effect on Lipids and Lipoproteins

LDL Particles

Enhanced VLDL Lipolysis in Insulin Resistance Patients with Hypertriglyceridemia on Fibrates

LPL = Lipoprotein Lipase

Fibrate induced increase in VLDL Lipolysis



Large LDL-P but ↓ small LDL-P

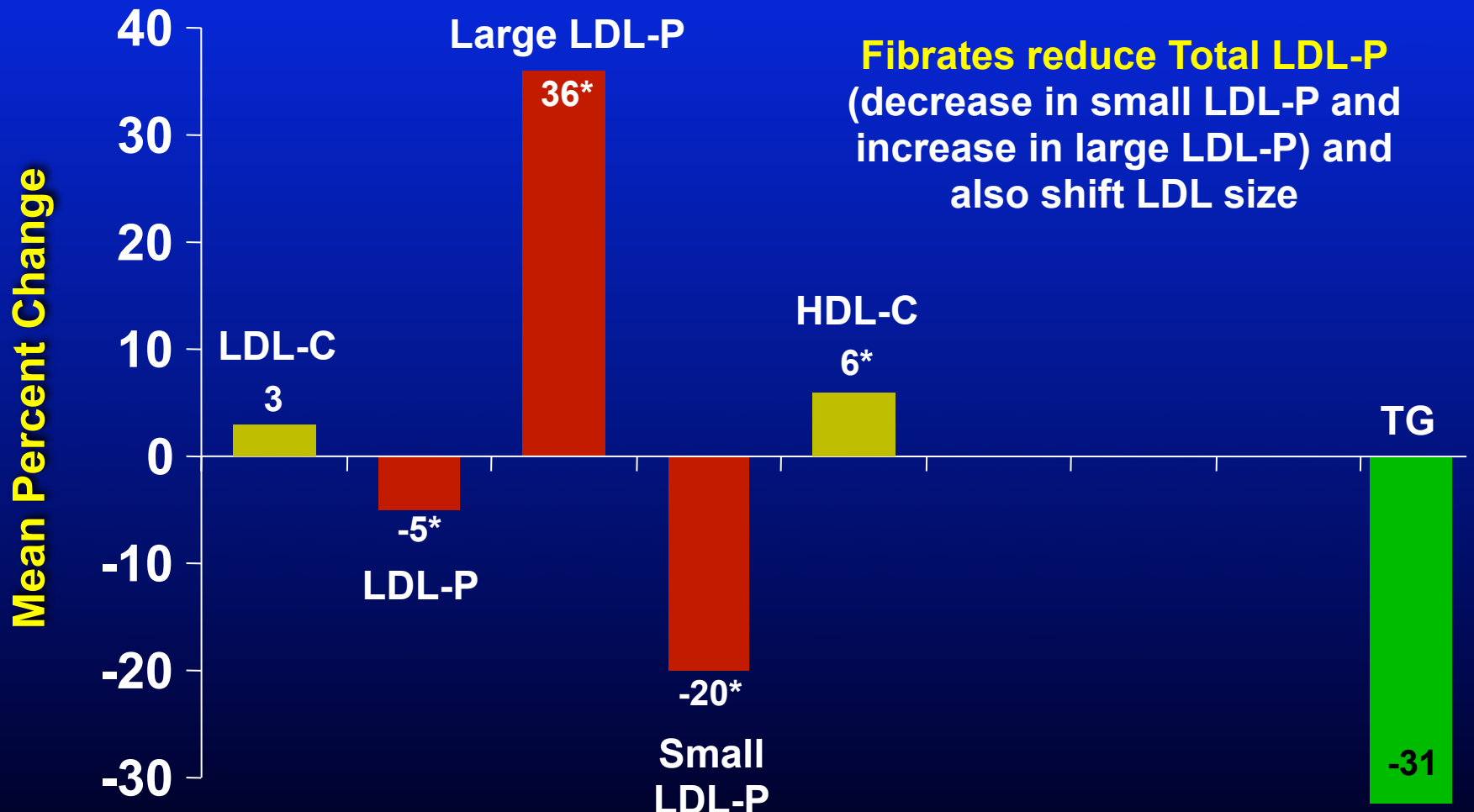
↓Overall Total LDL-P

↓ Production of VLDL-P and IDL-P

↓ apo B

Rapid VLDL Lipolysis: VLDLs disappear and LDLs appear: LDL-C may increase

The VA High-Density Lipoprotein Cholesterol Intervention Trial (VA HIT) Effects of Gemfibrozil



Fibrates reduce Total LDL-P (decrease in small LDL-P and increase in large LDL-P) and also shift LDL size

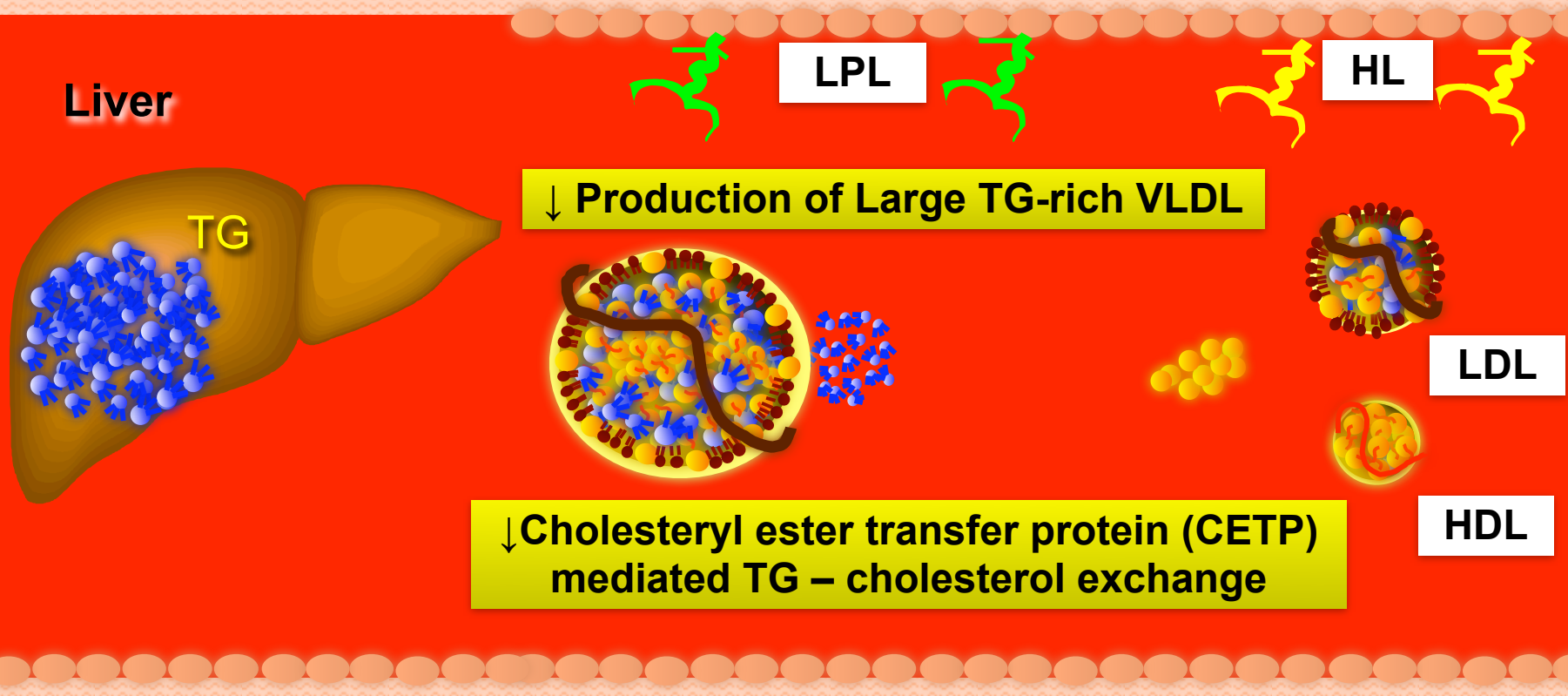
* p<0.001

Otvos JD et al Circulation 2006;113:1556-63

Decreased CETP Mediated CE/TG Exchange Creates Larger LDL & HDL

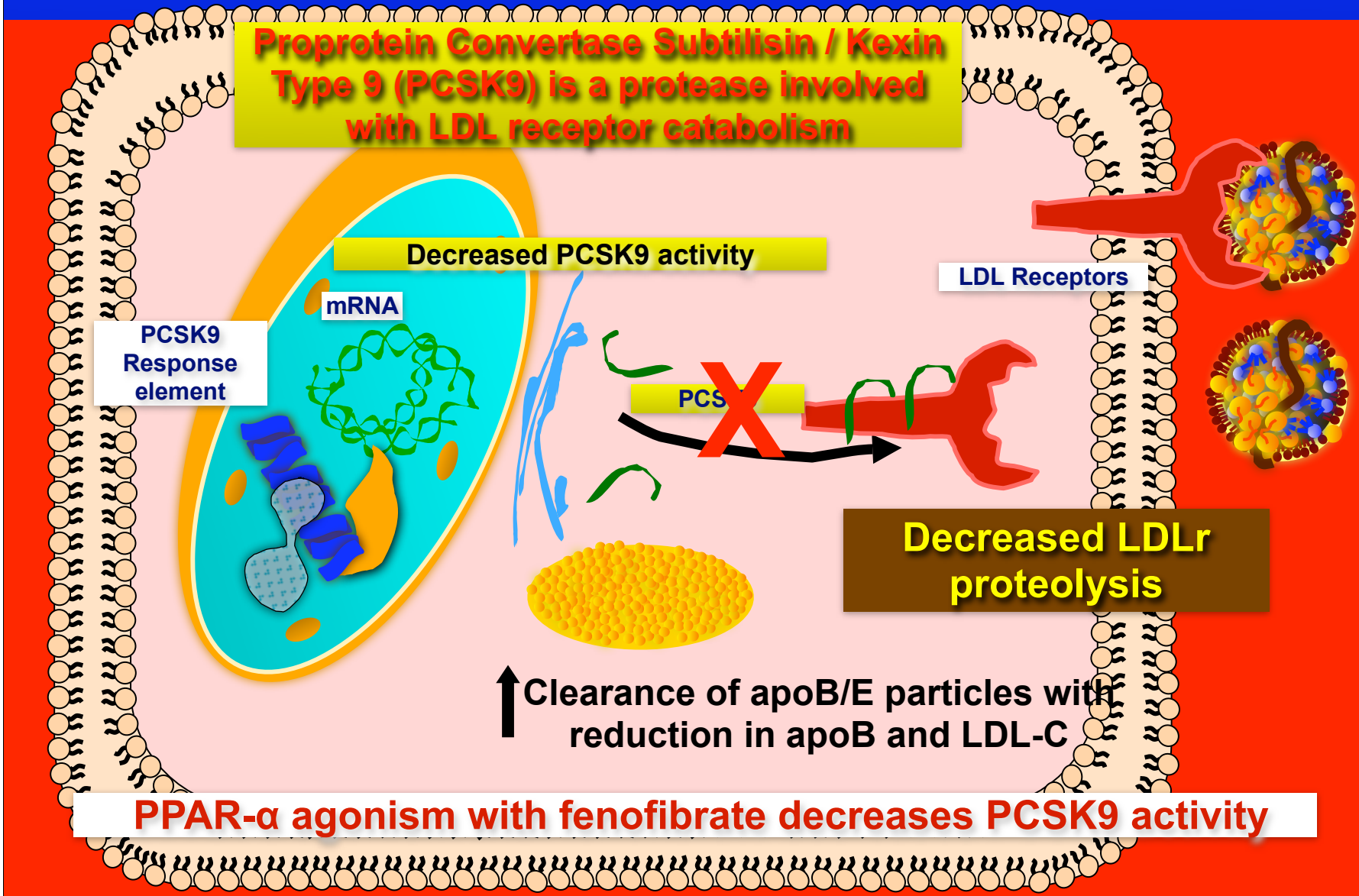
LPL = Lipoprotein Lipase

HL = Hepatic Lipase



LDLs and HDLs retain their CE and shift to a larger size: LDL-C & HDL-C may increase: LDLs become more amenable to LDLr endocytosis

Fenofibrate & LDL Receptors

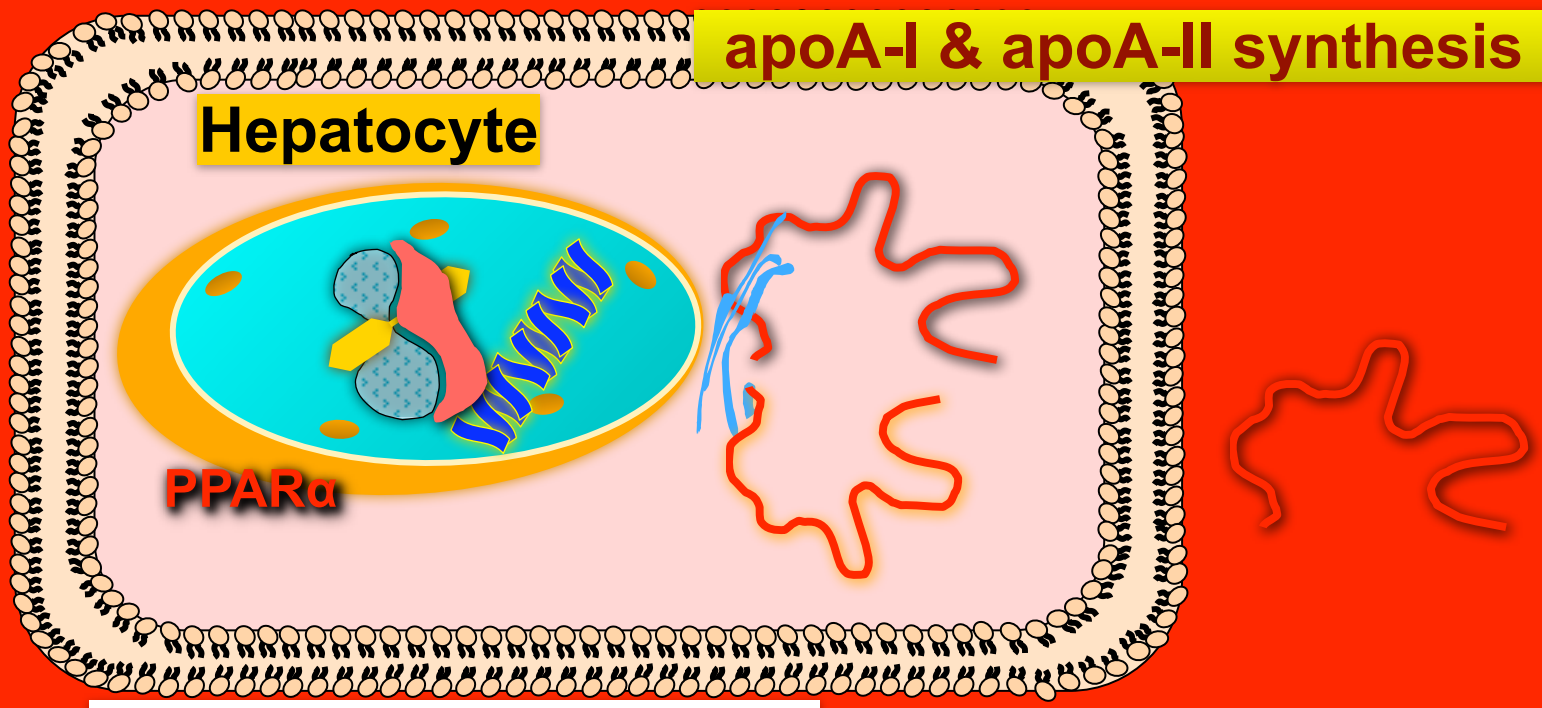


Lambert G Endocrinology 2006;147:4985-95

Fibrate Effect on Lipids and Lipoproteins

HDL Particles

Fibrates and HDL Particles



PPARα agonists like fibrates

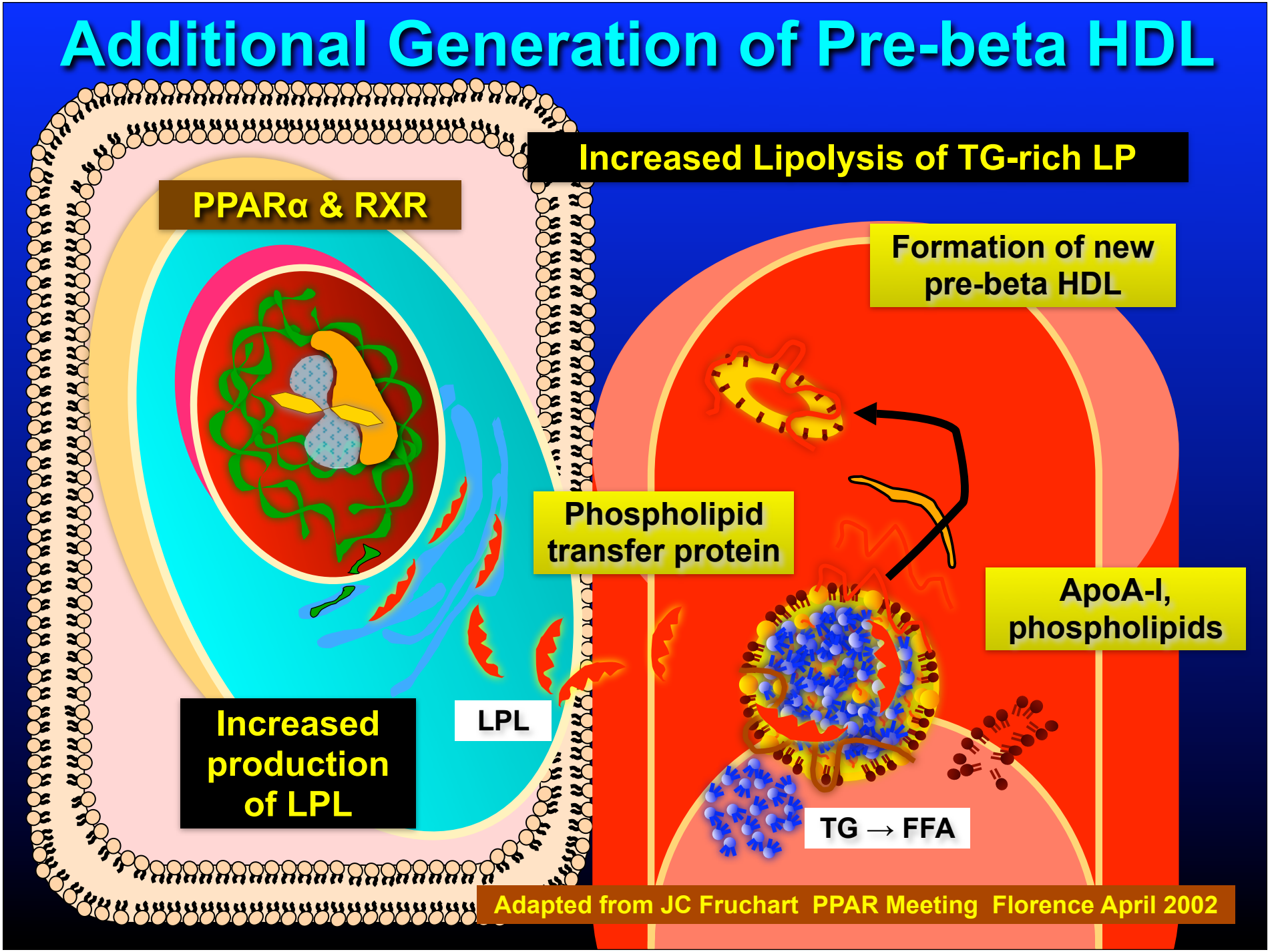
Forms heterodimer with RXR

ApoA-I,
A-II

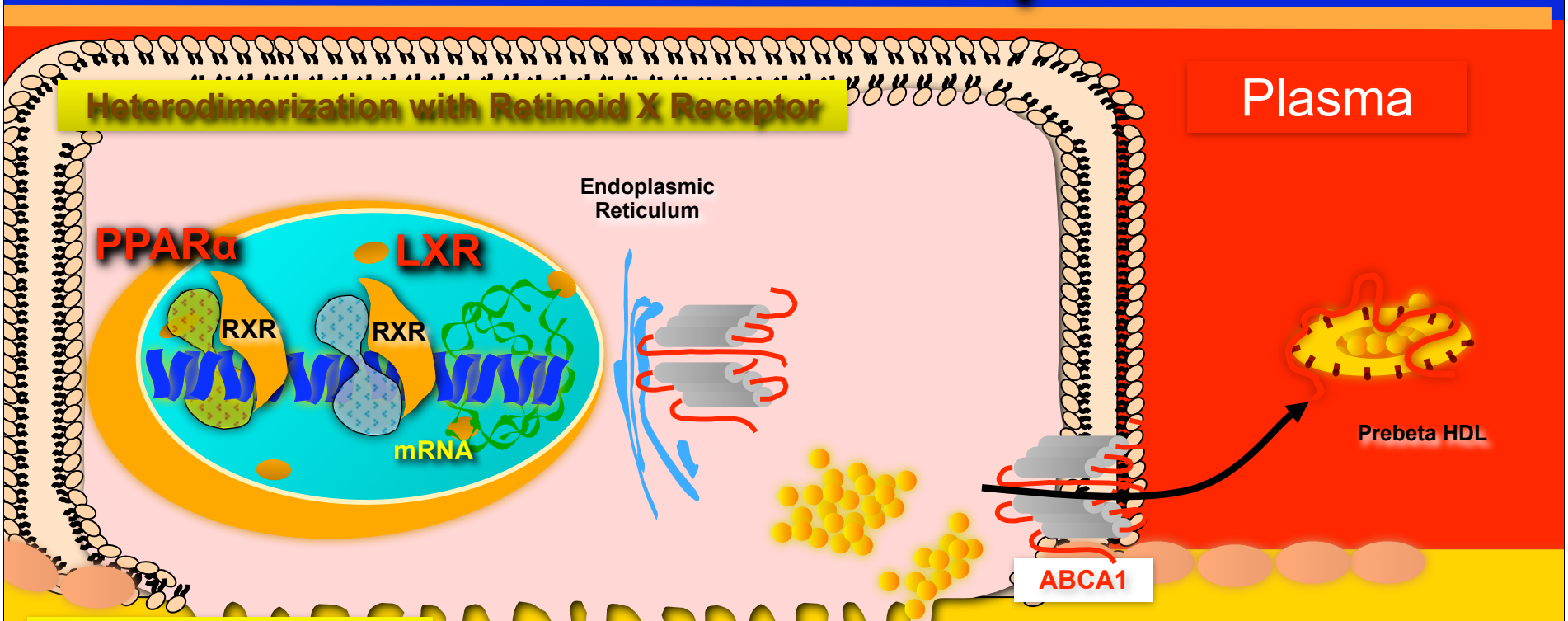
Hepatic Sinusoid

Acton S et al. Science 1996;217:518-520

Additional Generation of Pre-beta HDL



Regulating Cellular Cholesterol Levels PPAR-α and Liver X Receptors



The PPAR-α agonist Fenofibric acid increased transcription of ABCA1 gene in a liver X receptor– dependent manner.

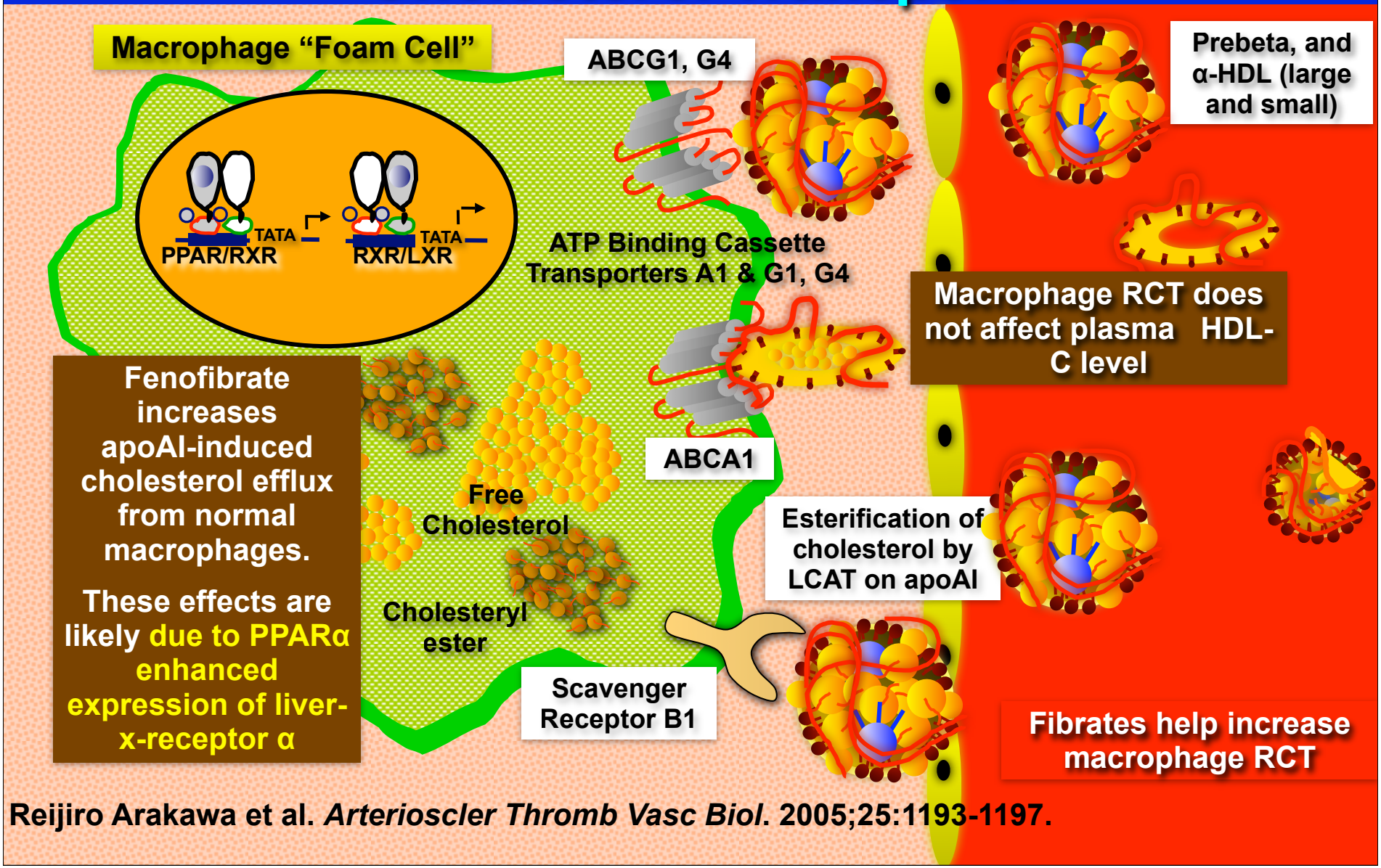
Liver X Receptors (LXR) regulate cellular sterol homeostasis and are upregulated as oxysterol levels rise

Hepatic LXR influences regulation of proteins involved with sterol homeostasis including ATP binding cassette sterol efflux transporters like ABCA1

Bile ductule

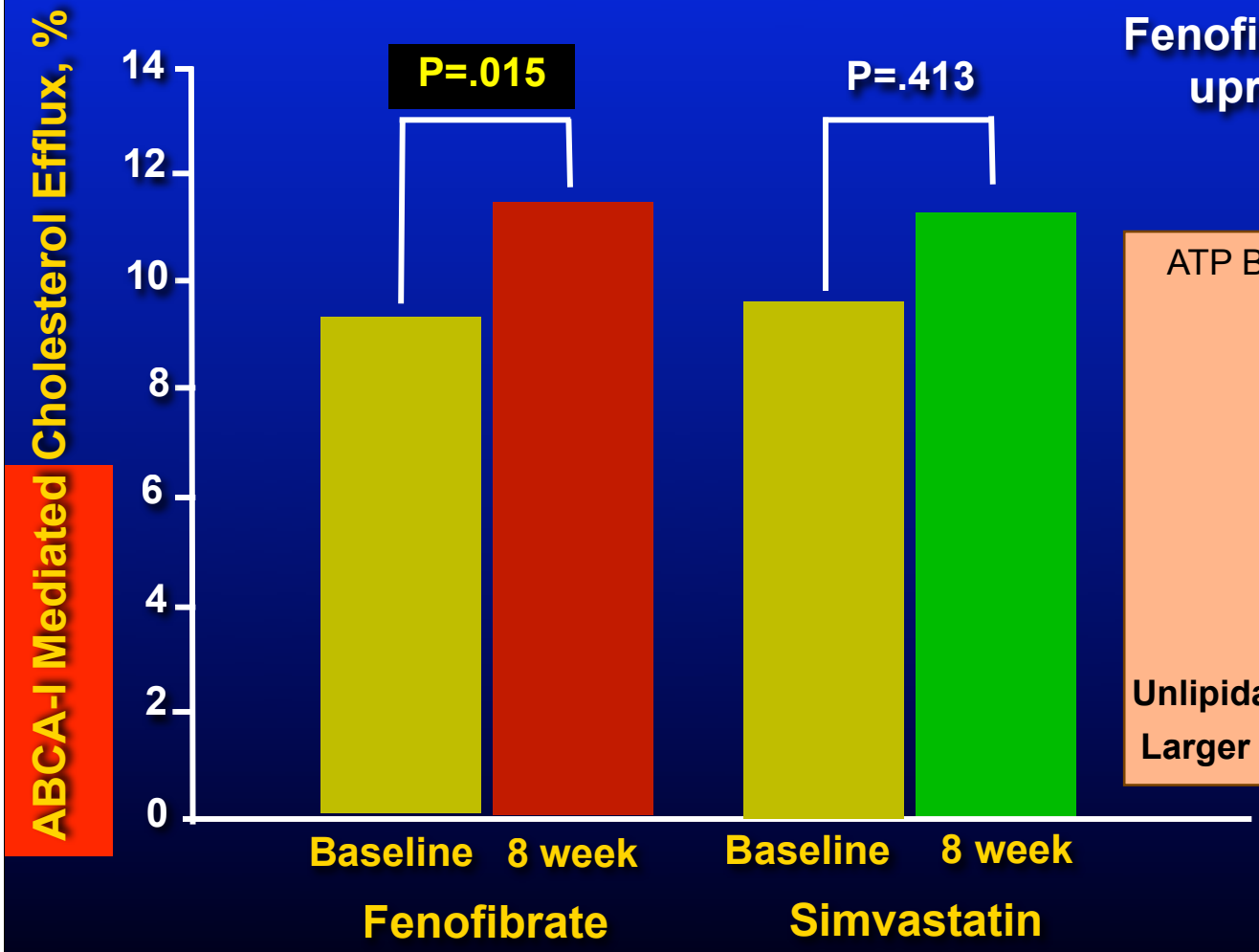
Arakawer R et al. ATVB 2005;25:1193-1197

Fibrates and Macrophage Reverse Cholesterol Transport

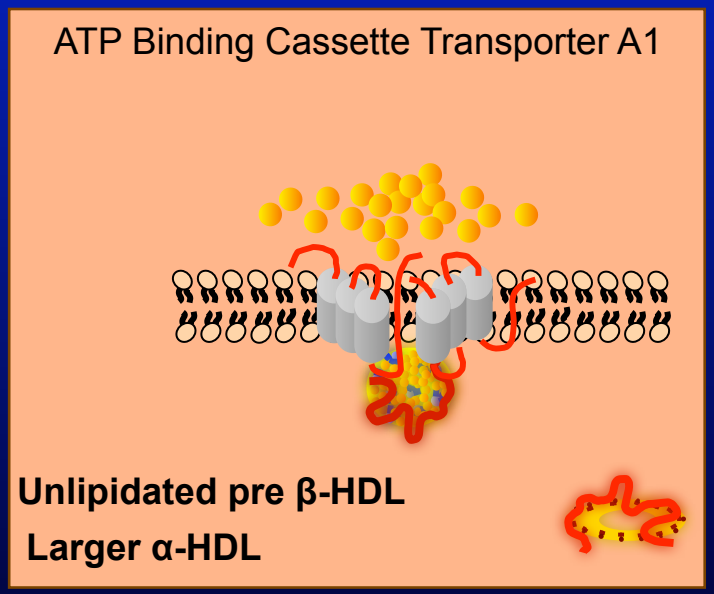


Reijiro Arakawa et al. *Arterioscler Thromb Vasc Biol*. 2005;25:1193-1197.

Effects of Fenofibrate and Simvastatin on HDL-related Biomarkers in Low-HDL Patients

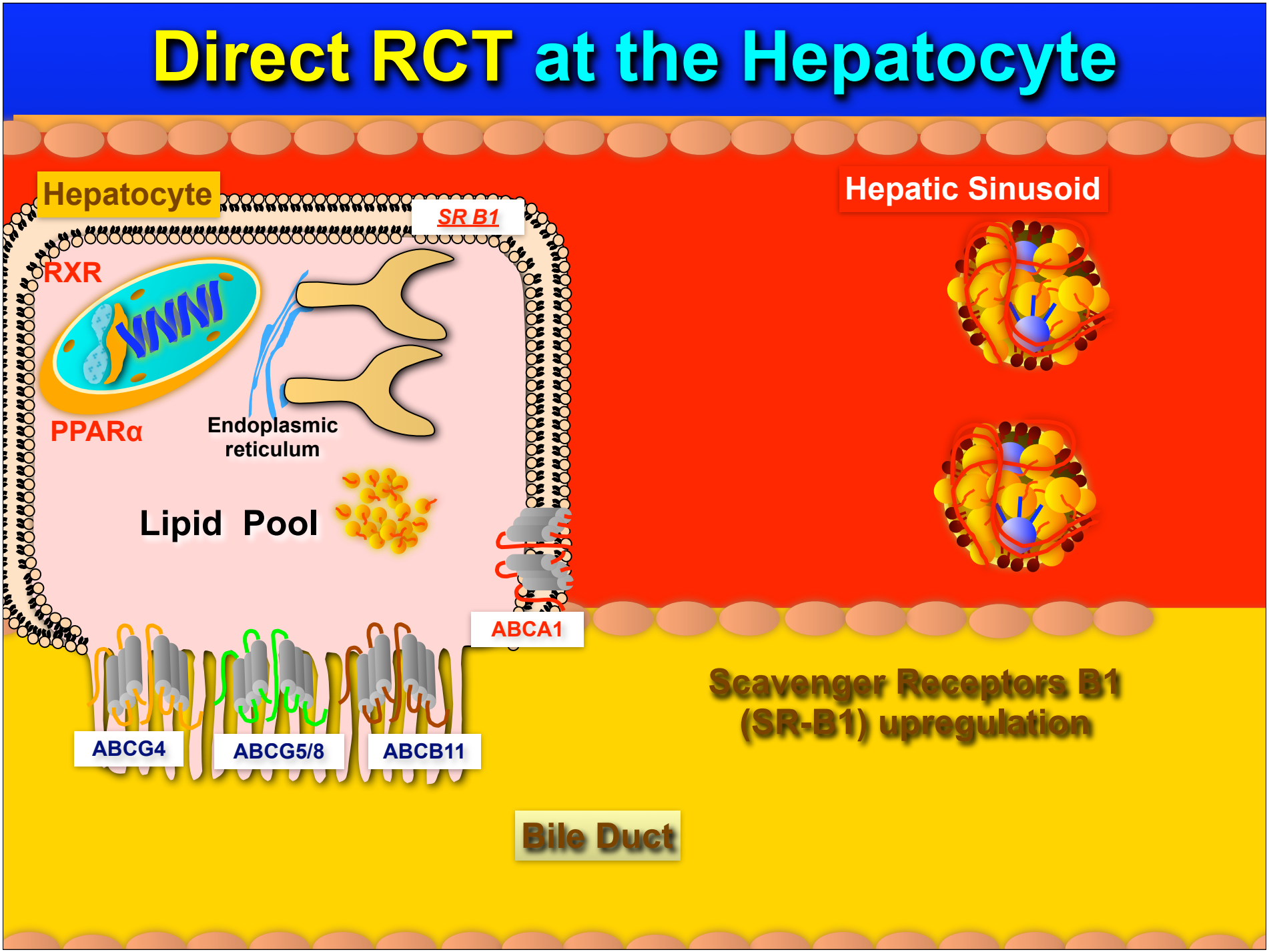


Fenofibrate, not the statin upregulates ABCA1

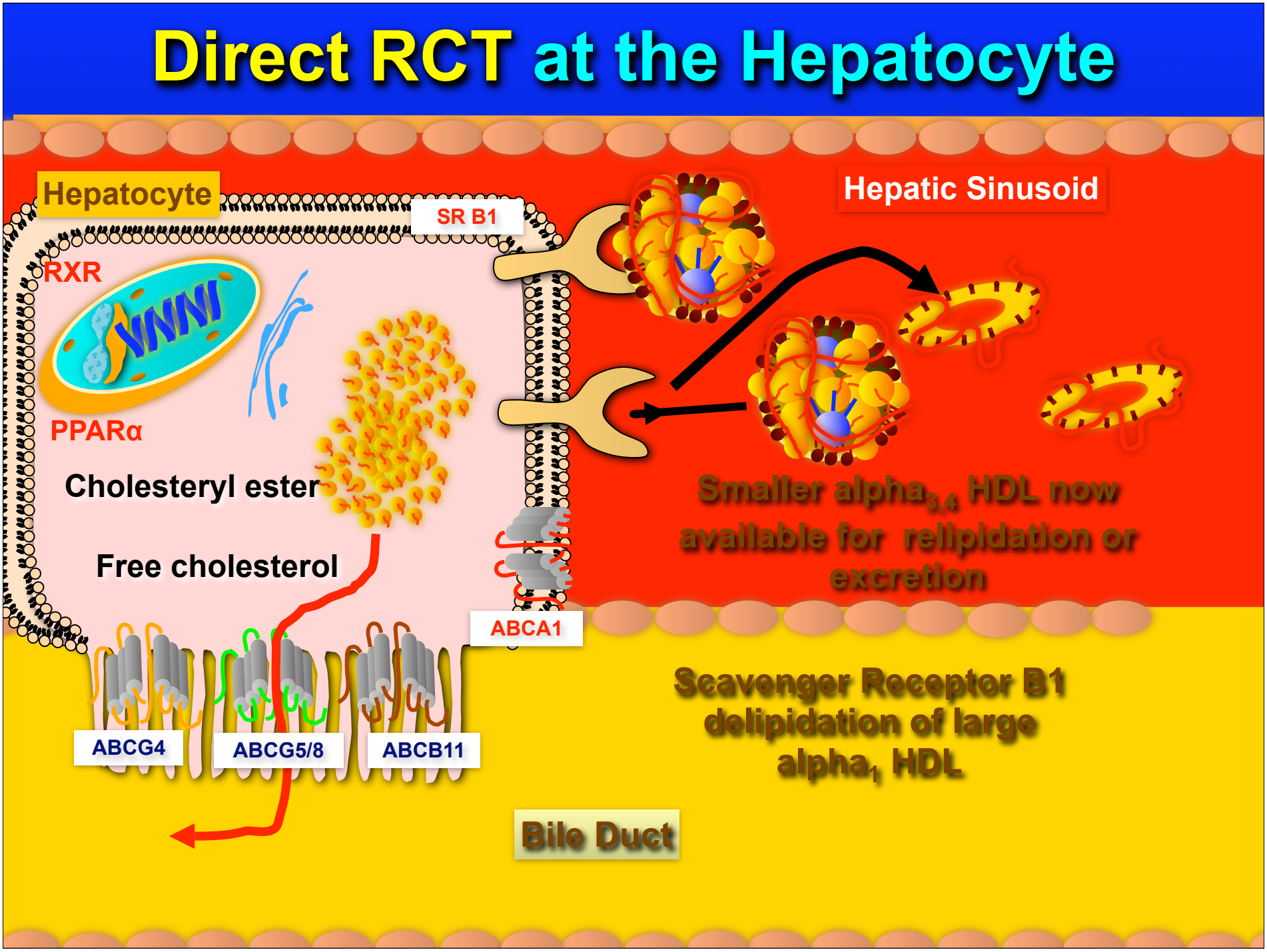


Franceschini G, et al. Atherosclerosis 195 (2007) 385–391

Direct RCT at the Hepatocyte

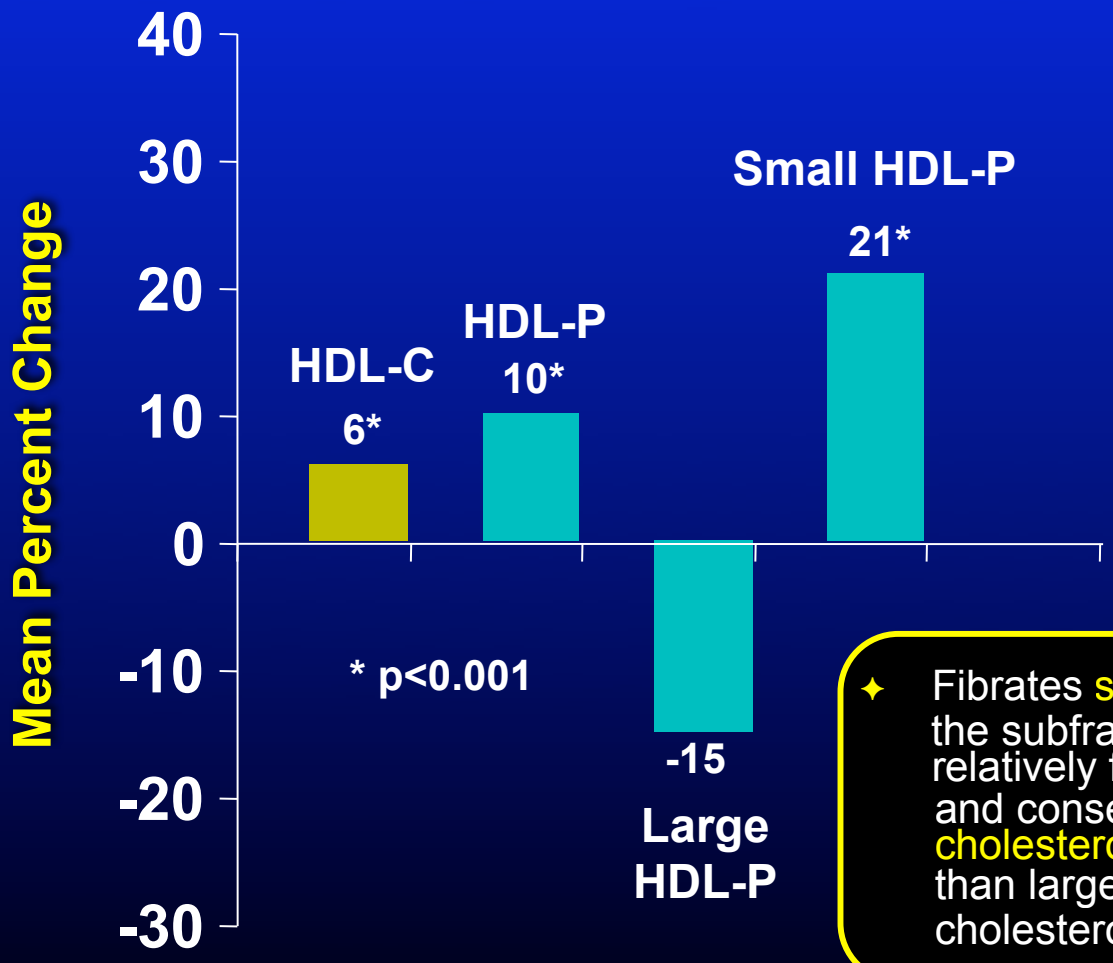


Direct RCT at the Hepatocyte



The VA High-Density Lipoprotein Cholesterol Intervention Trial (VA HIT)

Effects of Gemfibrozil On HDL Parameters



- Fibrates selectively increased **small HDL_3** the subfraction of HDL that is smaller and relatively free of cholesterol and consequently more likely to initiate free cholesterol efflux from peripheral tissues than large HDL_2 in the process of reverse cholesterol transport

Robbins, S et al. JAMA 2001;285:1585-1591

Otvos JD et al Circulation 2006;113:1556-63

Veterans Affairs HDL Intervention Trial (VA-HIT)

Explaining the Beneficial Effect of Gemfibrozil

Conclusions:

The effects of gemfibrozil on NMR-measured LDL and HDL particle subclasses, which are not reflected by conventional lipoprotein cholesterol measures, help to explain the demonstrated benefit of fibrate therapy in patients with low HDL cholesterol.

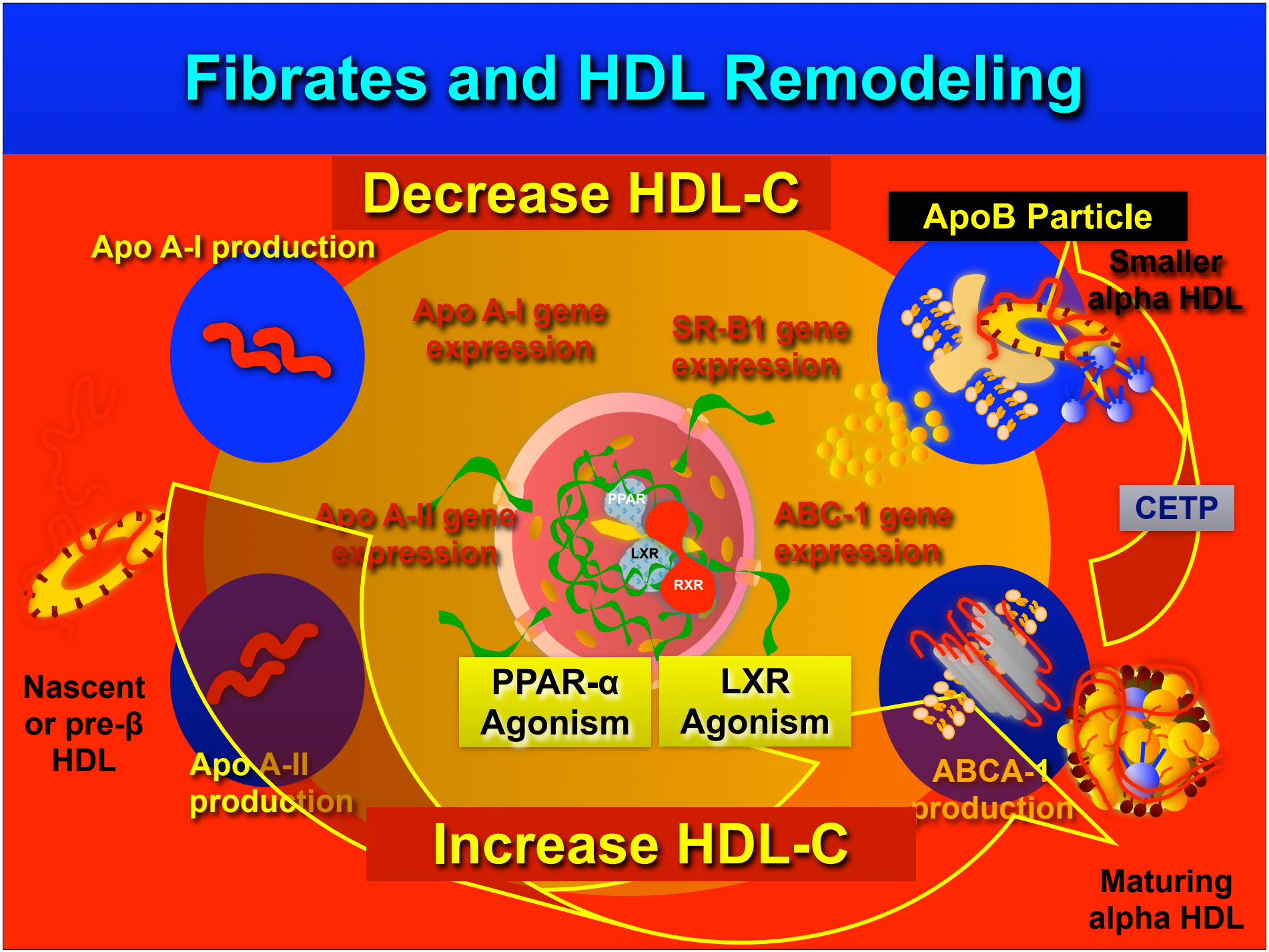
Otvos J et al Circulation 2006:113 on line

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Helsinki Cohort

- Relative to placebo, the difference in HDL-C at 5 years was not significant.
- Baseline HDL_2-C was 0.46 mmol/L in both groups and there was a gradual decrease over time in fenofibrate group (-21% at 2 years and -33% at 5 years, $p<0.001$).
- Baseline HDL_3-C levels were similar (0.73 vs. 0.72 mmol/L), with increase in fenofibrate group over time (8.1% at 2 years and 10.4% at 5 years, $p<0.001$).
- The respective changes were seen in total mass concentrations of HDL_2 and HDL_3 particles.

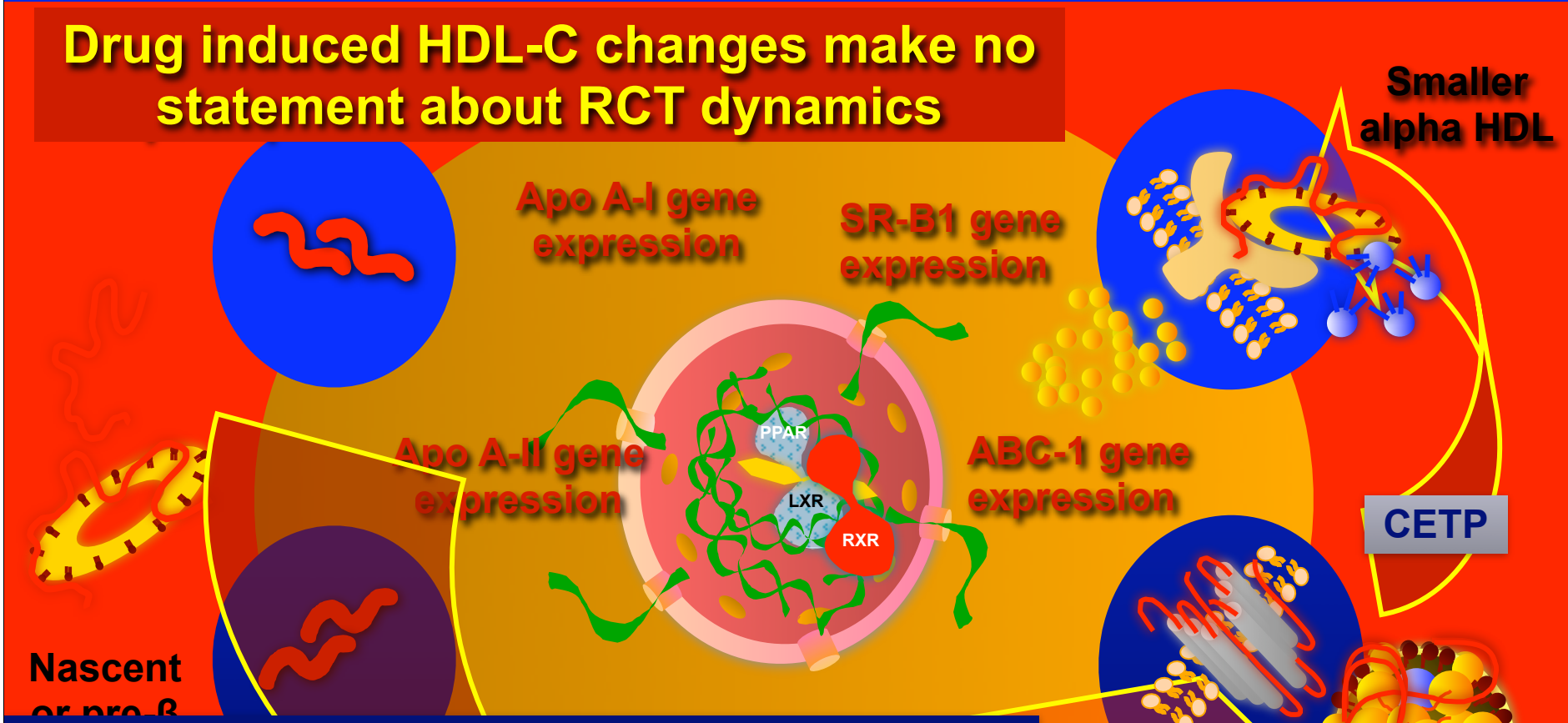
Hiukka A et al. Diabetologia 2007

Fibrates and HDL Remodeling

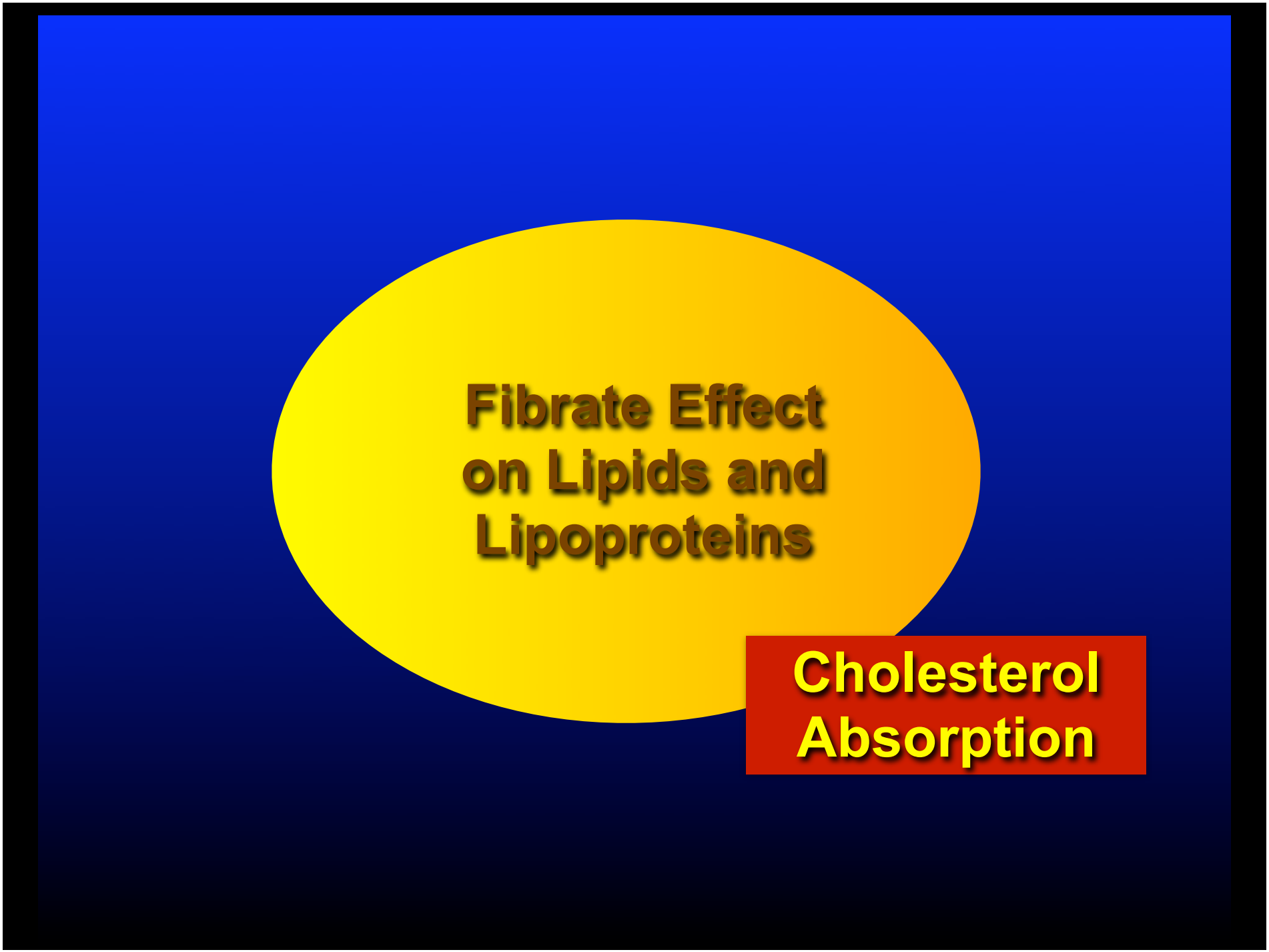


Fibrates and HDL Remodeling

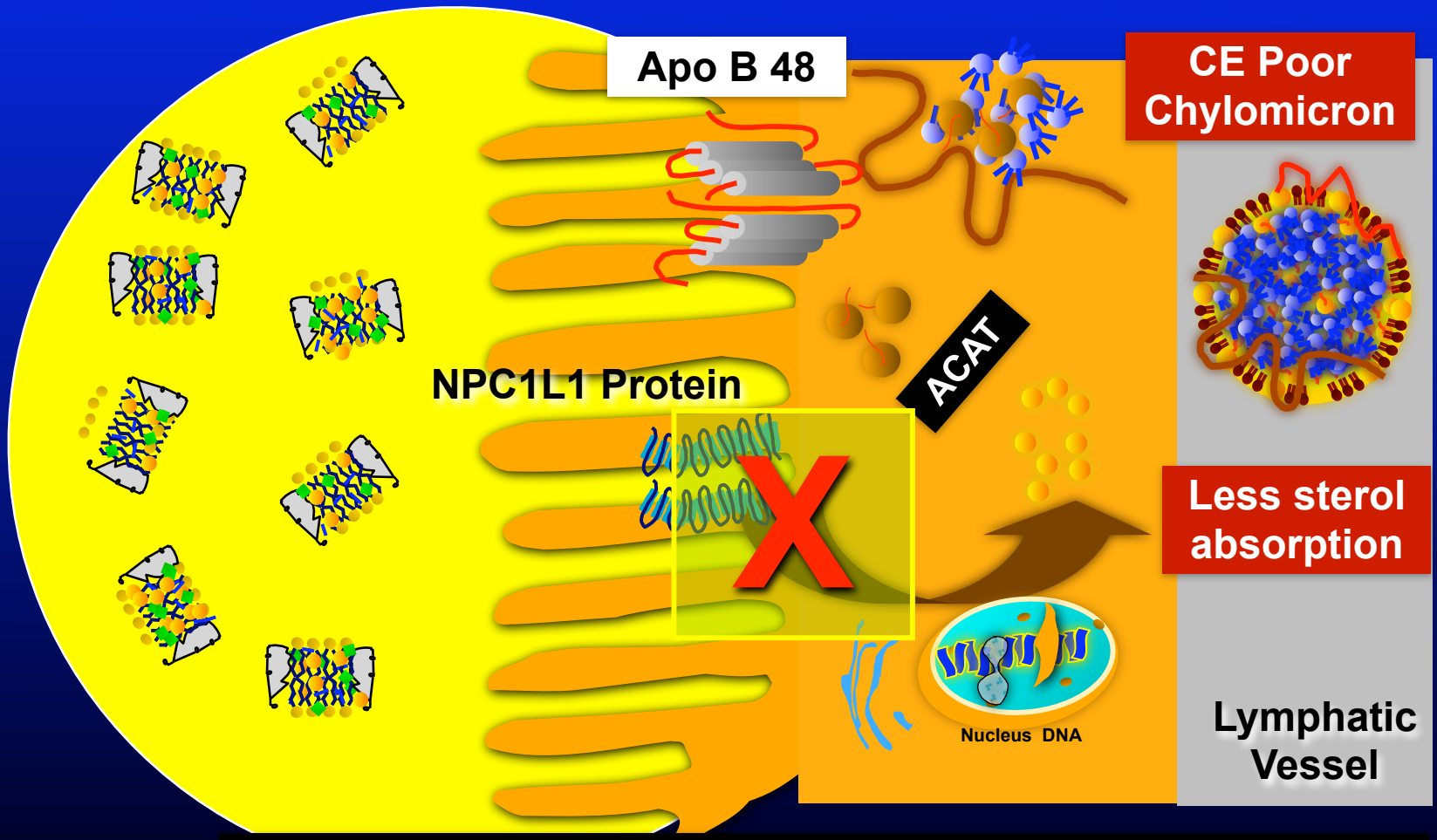
Drug induced HDL-C changes make no statement about RCT dynamics



Fibrates increase apoA-I and A-II production, upregulate ABCA1 & lipidate HDL and upregulate hepatic SR-B1 & CETP and ultimately delipidate HDLs: Significant increase in HDL-P and modest increase in HDL-C


Fibrate Effect
on Lipids and
Lipoproteins
Cholesterol
Absorption

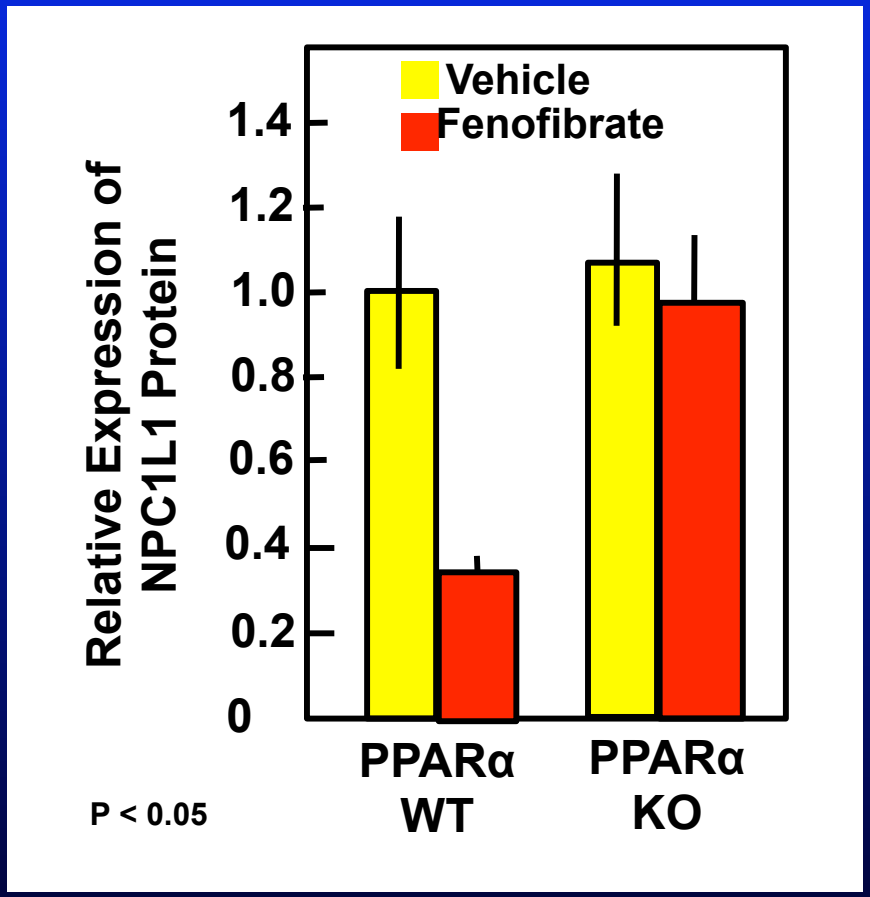
Fenofibrate Decreases Sterol Absorption

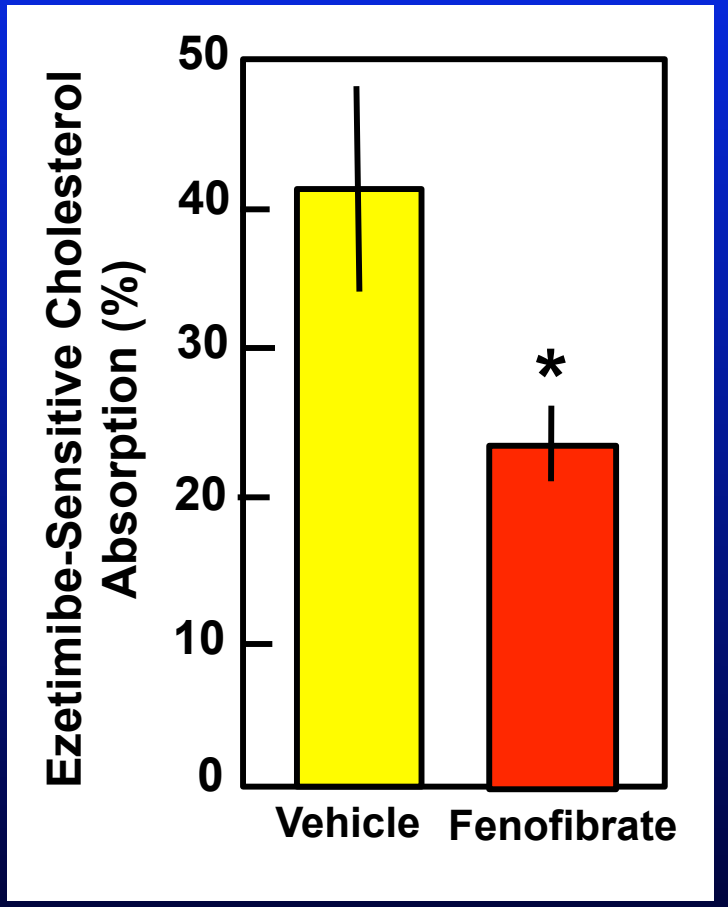


Valasek MA J Lipid Res 2007;48:2725-35

Fenofibrate, via PPARα agonism reduces expression of NPC1L1 & decreases sterol absorption

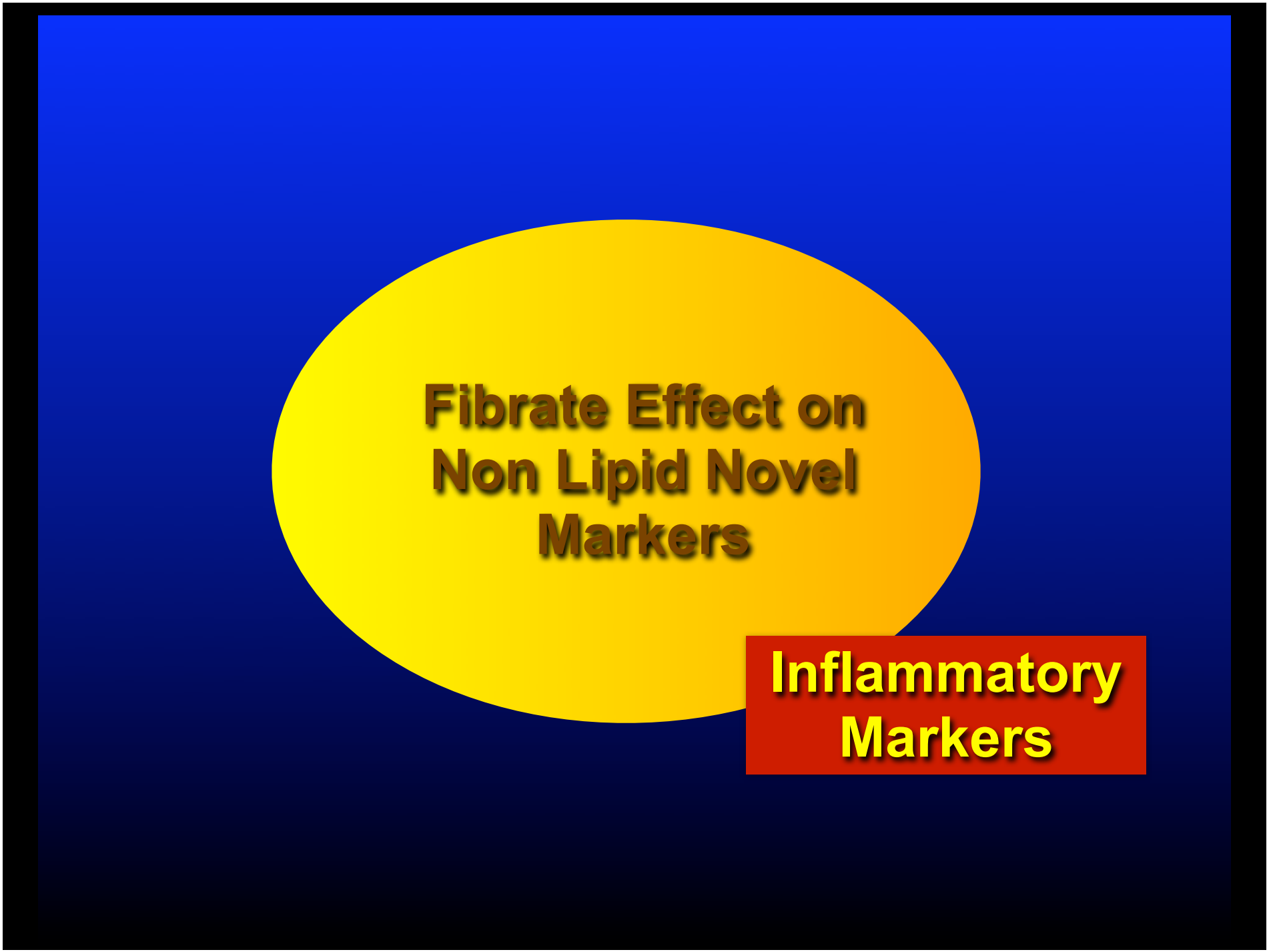
Fenofibrate Decreases Sterol Absorption





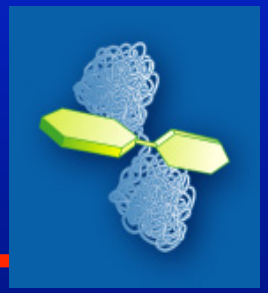
Specific activation of PPARα by fenofibrate decreases cholesterol absorption via an inhibitory effect on NPC1L1 expression in the proximal small intestine.

Valasek MA J Lipid Res 2007;48:2725-35


Fibrate Effect on Non Lipid Novel Markers
Inflammatory Markers

Anti-inflammatory and Immunomodulatory Effects of PPARα

Cell recruitment and activation



- PPARα activators decrease cell recruitment and activation

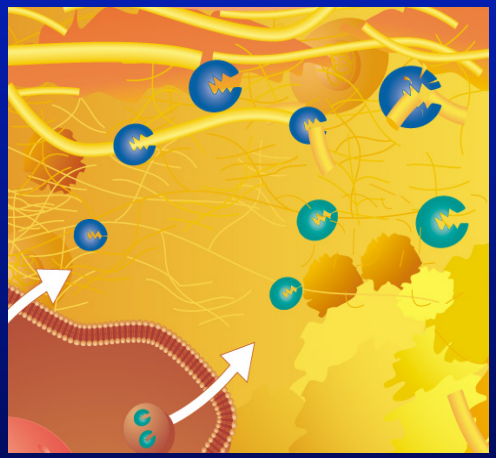
- **MPC-1**: Monocyte chemotactant protein-1
- **CCR2**: chemokine (c-c motif) receptor for CCL2 a monocyte & T-cell chemoattractant
- **VCAM-1 (CD106)**: Vascular cell adhesion molecule-1
- **ICAM-1 (CD54)**: Intracellular adhesion molecule

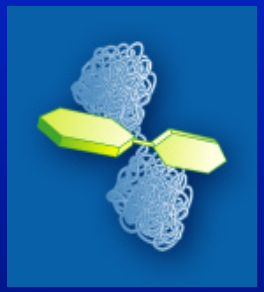
Marx N, et al. *Circulation*. 1999;99:3125-3131 and Circ Res. 2004;94:1168-1178

Anti-inflammatory and Immunomodulatory Effects of PPARα

↓Vasoconstriction

↓Cell migration





- PPARα activators inhibit oxidized LDL stimulation of endothelin-1 production in endothelial cells improving endothelial reactivity

↓**ET-1**: Endothelin-1, a potent vasoconstrictor

↑**eNOS**: Endothelial NO synthase

↓**Ets-1**: Endothelial cell transcription factor

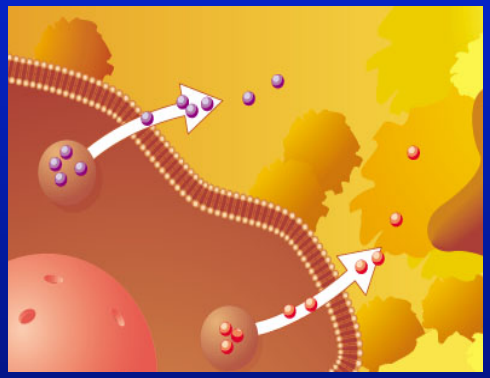
↓**TXS**: Thromboxanes

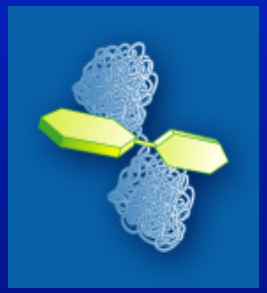
Martin-Nizard F, et al. *J Cardiovasc Pharmacol*. 2002;40:822-831.

Marx N, et al. Circ. 1999;99:3125-3131 and Circ Res. 2004;94:1168 1178

Anti-inflammatory and Immunomodulatory Effects of PPARα

Inflammatory response





- PPARα activators inhibit multiple inflammatory cytokines produced by T-lymphocytes by preventing Th0 cells from differentiating to more deleterious Th1 cells

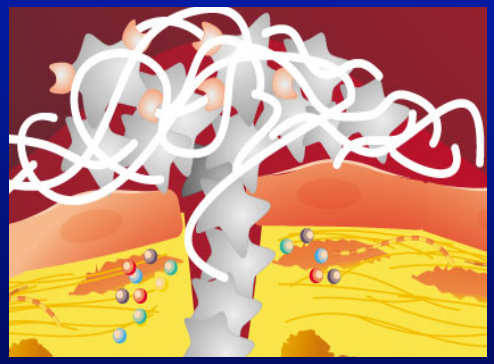
↓**TNFα:** tumor necrosis factor-α
↓**IFNγ:** Interferon
↓**CRP:** C-reactive protein
↓**COX-2:** Cyclooxygenase-2 (affects prostaglandins)
↓**TF:** Tissue factor in monocytes & macrophages
↓**Fibrinogen**
↓**Lp-PLA$_2$:** Lp-associated Phospholipase A$_2$
↓**IL-1, IL-2, IL-6:** Interleukins (affect VSMC activation)
↓**MMPs:** Metalloproteinases in macrophages

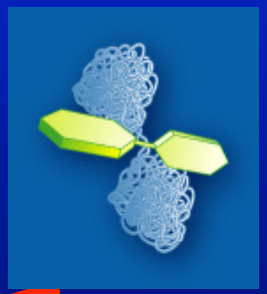
Marx N, et al. *Circ Res.* 2002;90:703-710. & Circ Res. 2004;94:1168-1178

Anti-inflammatory and Immunomodulatory Effects of PPARα

↓ Thrombosis

↑ Plaque stability





- PPARα activators have antithrombotic effects by inhibiting tissue factor expression in monocytes and macrophages

↓**MMP-9**: Metalloproteinase-9

↓**TXS**: Thromboxanes

↓**PAF**: Platelet acetyl hydrolyzing factor

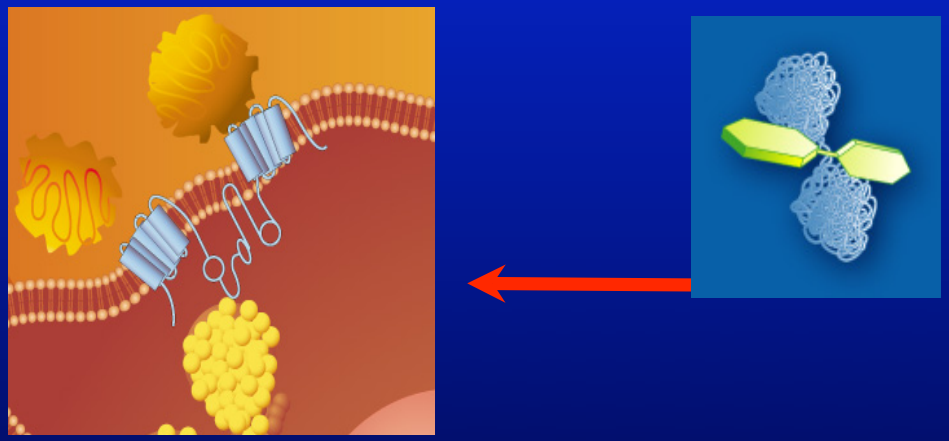
↓**TF**: Tissue factor

Neve BP, et al. *Circulation*. 2001;103:207-212.

Marx N, et al. *Circulation*. 1999;99:3125-3131 and Circ Res. 2004;94:1168-1178

Anti-inflammatory and Immunomodulatory Effects of PPARα

↑ Cholesterol Efflux
↓ Foam Cell Formation



- PPARα activators decrease uptake of ox-LDL in macrophages and increase macrophage RCT

↓**CD36**: Scavenger receptor

↓**SR-A**: Scavenger receptor-A

↓**LRP**: LDL receptor related protein (apoB48 or remnant receptor

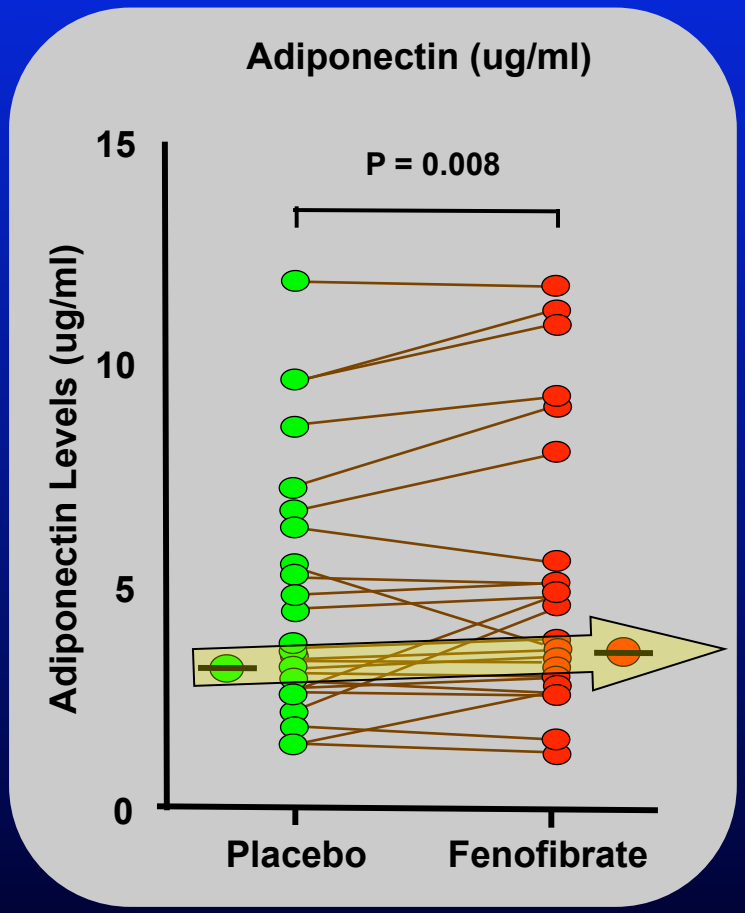
↓**ACAT-1 activity**: increases free cholesterol for efflux

↑**ABCA1**: ATP Cassette transporter A1

↑**SR-B1**: Scavenger receptor-B1

Neve BP, et al. Circ. 2001;103:207-212.
Marx N, et al. Circ. 2001;103:213-219
& Circ res 2004;94:1168-1178.

Fenofibrate & Adiponectin in Patients with Hypertriglyceridemia



CONCLUSIONS: Fenofibrate therapy significantly improved percent flow-mediated dilator response to hyperemia, reduced inflammation marker levels, increased adiponectin levels, and improved insulin sensitivity in hypertriglyceridemic or metabolic syndrome patients.

Koh, KK et al. Diabetes Care 2005;28:1419-24

Fibrates Inhibit Aldose Reductase

- Synthesis and accumulation of sorbitol in cells due to aldose reductase (AR) activity is implicated in secondary diabetic complications
- Fibrates (bezafibrate, gemfibrozil, clofibric acid, ciprofibrate and fenofibrate) inhibit AR activity
- AR participates in glucose metabolism as it is the first enzyme of the polyol pathway that converts glucose to its sugar alcohol, sorbitol
  - The polyol pathway has been implicated in oxidative stress

With hyperglycemia the second step produces elevated cytosolic NADH/NAD^+ ratio leading to cellular ischemia

The polyol pathway is implicated in increased oxidative stress which plays a role in causation of diabetic complications

Balendiran GK & Rajkumar B Biochem Pharm. 2005;70:1653-1663