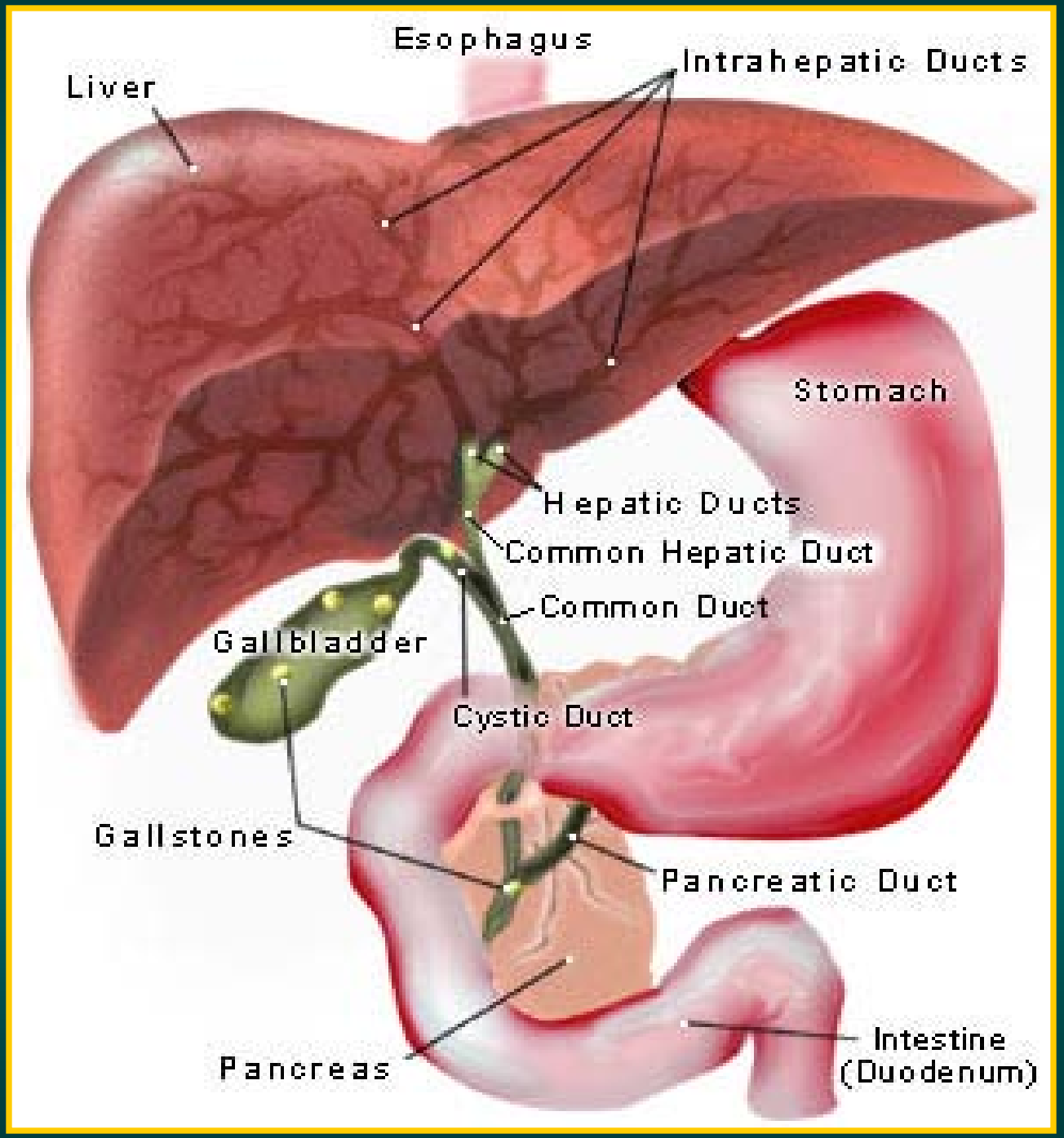



# Future stars:

# LXR

## et al.

# Simplified overview of current understanding of the metabolic roles of the 3 PPAR isoforms

| | PPARα | PPARγ | PPARδ |
|---|---|---|---|
| Sites of highest expression | Liver, kidney, heart | Adipose tissue, macrophages | Adipose tissue, skin, brain, but widespread |
| Cellular processes activated | Fatty acid β-oxidation, lipoprotein synthesis, amino acid catabolism | Adipocyte differentiation, triglyceride synthesis | Fatty acid β-oxidation |
| Physiological function | Coordination of metabolic response to fasting | Differentiation of adipocytes, FA trapping | Muscle fiber type determination? |
| Examples of target genes | *Carnitine palmitoyl transferase I, HMG CoA synthase 2, apoA-I* | *Fatty acid–binding protein 4, lipoprotein lipase, adiponectin* | *Acyl-CoA oxidase, carnitine palmitoyl transferase I* |
| Metabolic phenotype of knockout mice | Fasting hypoglycemia, hypothermia, hypoketonemia, and hepatic steatosis | –/– Lethal, –/+ more insulin sensitive at baseline | Reduced base-line adiposity; increased obesity on high-fat feeding |

*Semple et al. 2006*

# Double or triple PPAR ligands

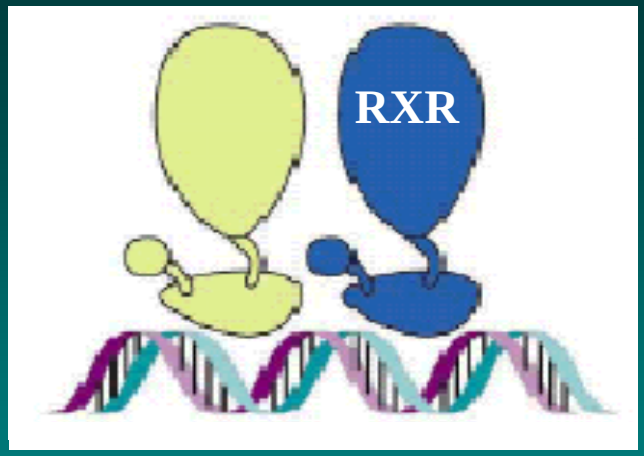
| Subtype | Tissue | Function | Effect of modulators on | | | |
|---|---|---|---|---|---|---|
| | | | Glucose | LDL-C | HDL-C | Triglycerides |
| Alpha | Liver, kidney, heart, muscle | Lipid metabolism | None | Lowers | Raises | Lowers |
| Delta | Broad distribution | Cholesterol transport | None | Lowers | Raises | Lowers |
| Gamma | Adipose | Glucose homeostasis, fat cell differentiation | Lowers | Raises | Raises | Variable |

**Double (activation of PPARα and PPARγ):**
**- clinical trial of III phase - abandoned.**

**Triple (activation of PPARα, PPARβ and PPARγ):**
**- preclinical studies and clinical pharmacokinetic studies on volunteers - abandoned.**

**Side effects of PPARγ ligands:**
**- gain of weight (because of adipogenesis) – but paradoxically it is related with insulin-sensitivity**
**- edema (because increase in VEGF expression and NO synthesis leading to vasodilatation).**

# LXR (Liver X receptor)




- Adopted orphan receptor (heterodimer with RXR)

- Sensor of cholesterol expressed in all tissues.

- Involved in the regulation of cholesterol metabolism.

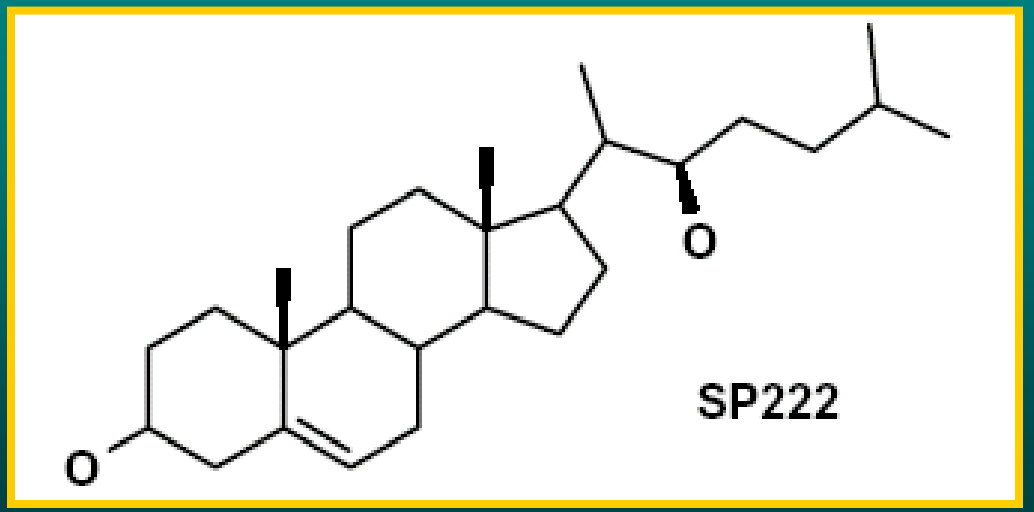
- LXR ligands are intermediates and end-products of sterol metabolism:

  * 22(R)-hydroxycholesterol

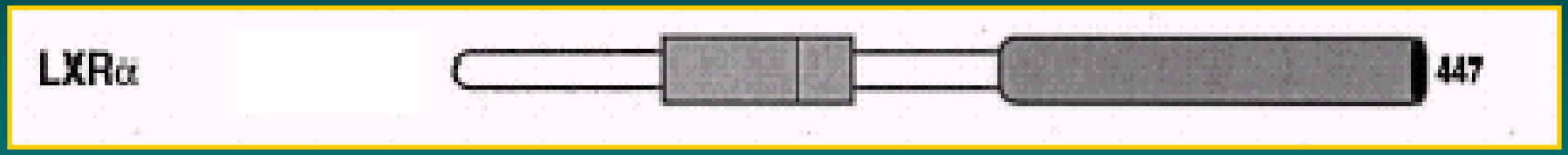
  * 24(S)-hydroxycholesterol

  * 27-hydroxycholesterol

  * 24(S),25-epoxycholesterol



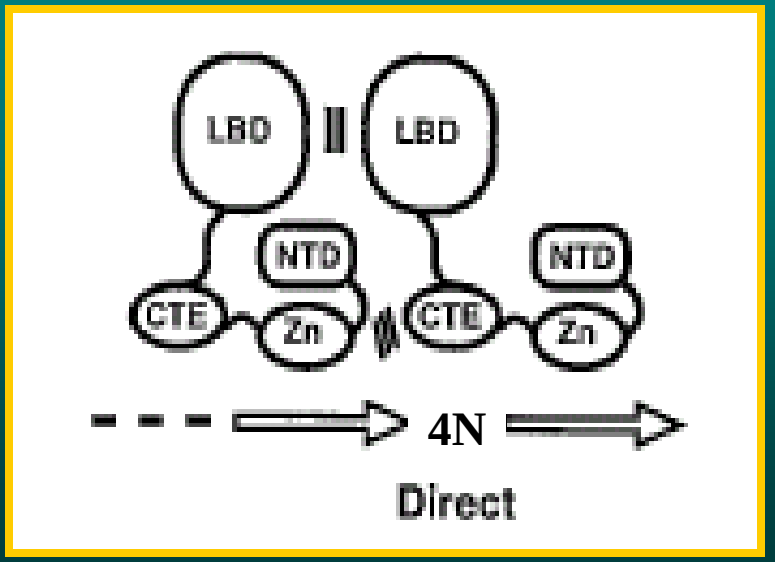
# LXR (Liver X receptor)



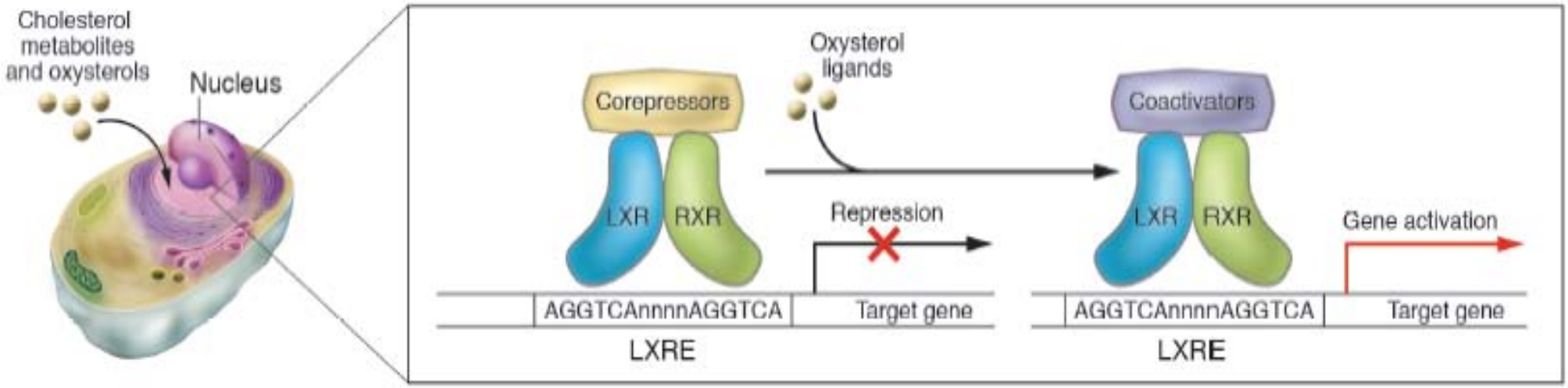

- Both known isoforms of LXR (LXRα i LXRβ) have similar structure, high homology of sequence, similar affinity to consensus sequence and sensitivity to ligands. They differ in tissue expression pattern.

* LXRα - strongly expressed in hepatocytes, macrophages, and adipocytes.
* LXRβ - ubiquitously expressed.

- LXR binds to DR4 sequence as a heterodimer with RXR
It is a permissive heterodimer, thus can be activated
both by ligands of LXR and ligands of RXR.



# LXR




- LXRs are cholesterol-sensing transcription factors.
- Within the nucleus, LXR/RXR heterodimers are bound to LXREs in the promoters of target genes and in complex with corepressors (e.g., SMRT, N-CoR).
- In response to the binding of oxysterol ligands, the corepressor complexes are exchanged for coactivator complexes, and target gene expression is induced.

# Role of LXR – LXRα KO mice

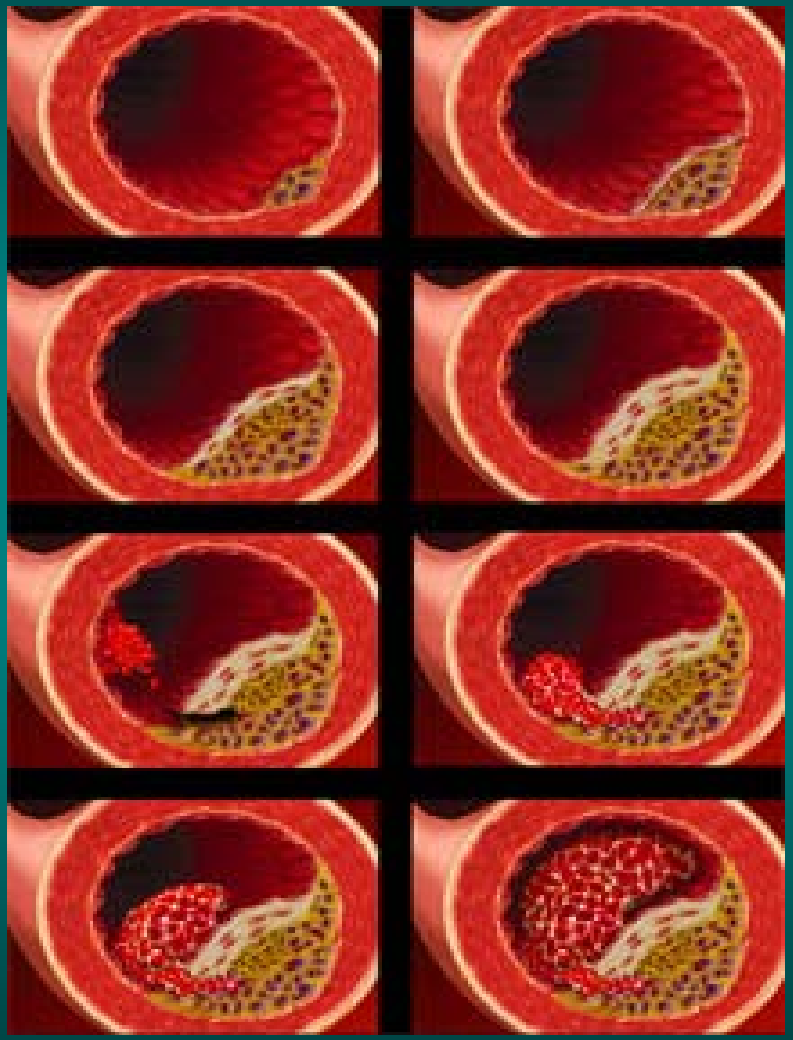
- Mice LXRα knockout have:

  * very high level of LDL
  * very low HDL.

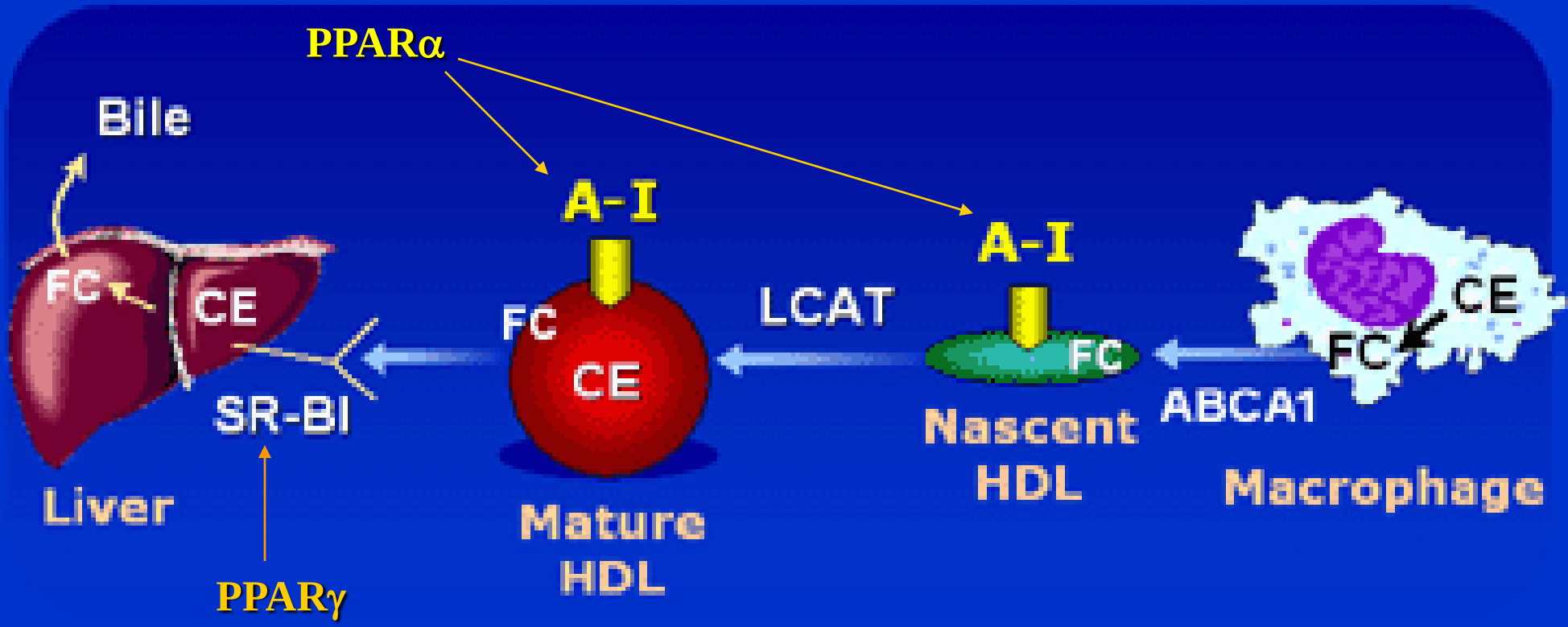
- They have many foam cells in different tissues.

- Mice have also stronger inflammatory reactions.

- If fed on cholesterol enriched diet, they have cholesterol accumulation in the liver (because of low expression of CYP7A and disturbed cholesterol metabolism) with consequent hepatic failure.



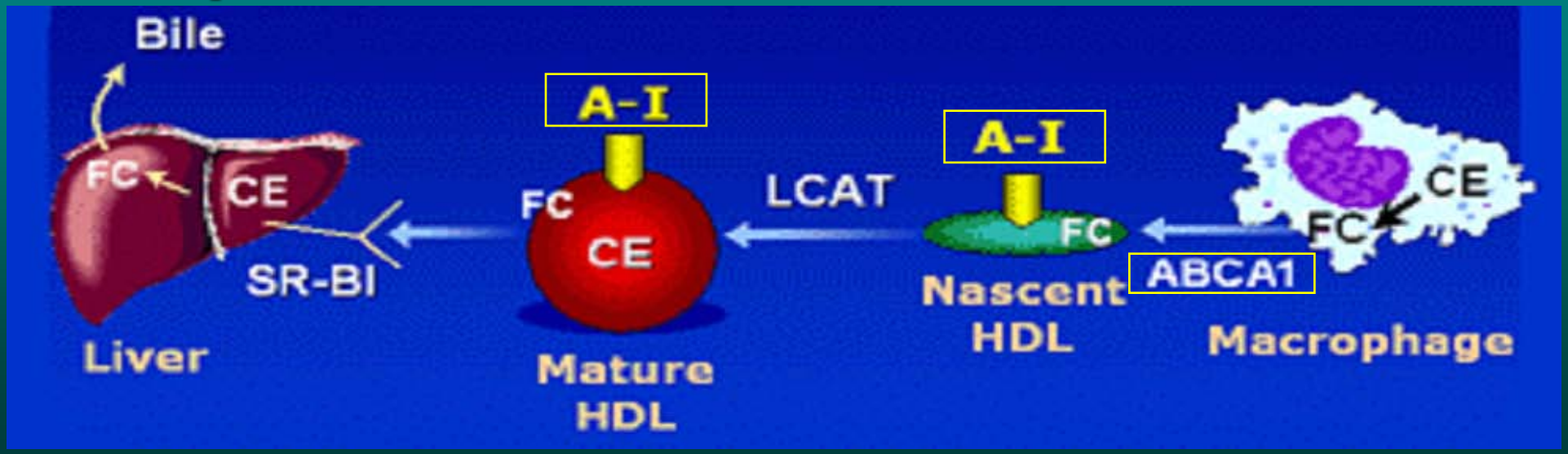
# HDL and Reverse Cholesterol Transport




**HDL is believed to protect against atherosclerosis at least in part through the process of reverse cholesterol transport, whereby excess free cholesterol (FC) is removed from cells in peripheral tissues, such as macrophages within the arterial wall, and returned to the liver for excretion in the bile. FC is generated in part by the hydrolysis of intracellular cholesteryl ester (CE) stores. Several key molecules play a role in reverse cholesterol transport, including ATP-binding cassette protein A1 (ABCA1), lecithin:cholesterol acyltransferase (LCAT), and scavenger receptor class-B, type I (SR-BI).**

# Some target genes for LXR

- CYP7A1 – enzyme determining the rate of synthesis of bile acids.
- **ABCA1** – transmembrane protein transporting different molecules, including cholesterol using energy from hydrolisis of ATP.
- ApoAI - lipoprotein
- LPL – catalyses hydrolysis of triglicerydes in lipoproteins.
- CEPT - transport of cholesterol esters from HDL to VLDL

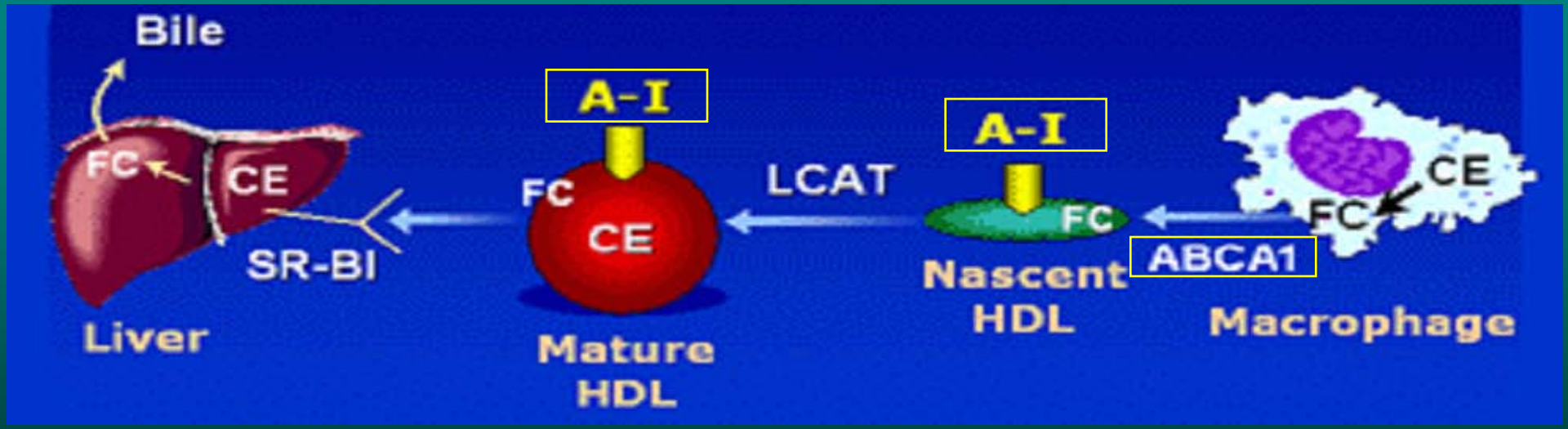


# Role of LXR

- Treatment of mice with ligands for LXR leads to:

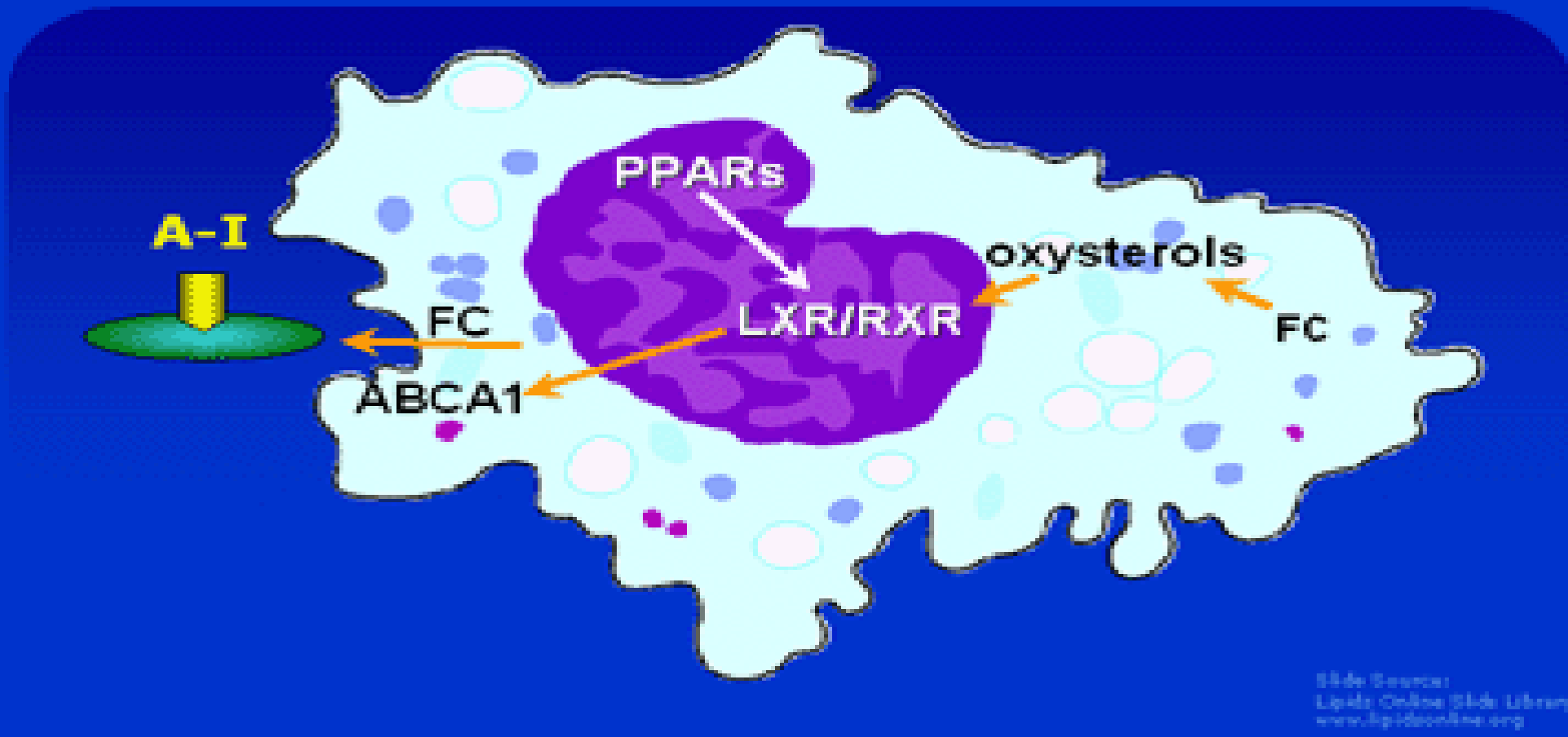
  * Increased level of HDL.
  * Increased reverse transport of cholesterol.
  * Decreased cholesterol absorpion in the intestine.
  * Inhibition of proinflammatory cytokines' synthesis in macrophages.
  * Decreased development of atherosclerotic plaque.

- **LXR is induced in response to activation of PPARα and PPARγ.** It consists PPRE in the promoter.

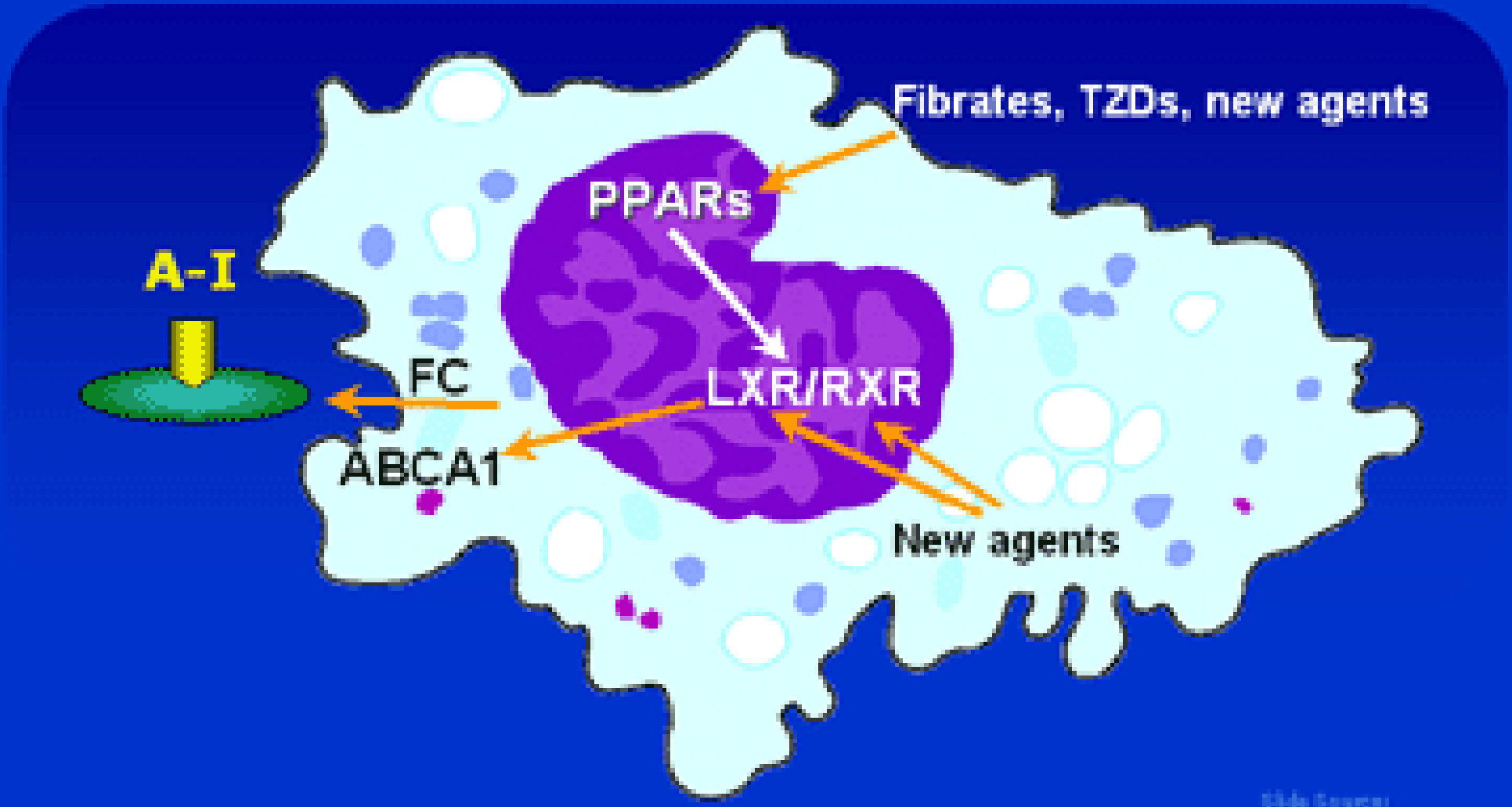



**ABCA1** – transmembrane protein transporting different molecules, including cholesterol using energy from hydrolisis of ATP; **ApoAI** - apolipoprotein AI, important for HDL formation;

**Regulation of cholesterol efflux in the macrophage. The cellular transporter ABCA1 is a critical protein that transports excess free cholesterol (FC) out of the cell to an acceptor, lipid-poor apo A-I. HDL ABCA1 gene transcription is regulated by the LXR. Cellular oxysterols appear to be one of the endogenous ligands for LXR and promote the transcription of ABCA1. Oxysterols are generated from free cholesterol. Presumably, this represents a homeostatic mechanism by which macrophages rid themselves of excess free cholesterol. LXR gene transcription is also influenced by both PPAR-α and PPAR-γ.**



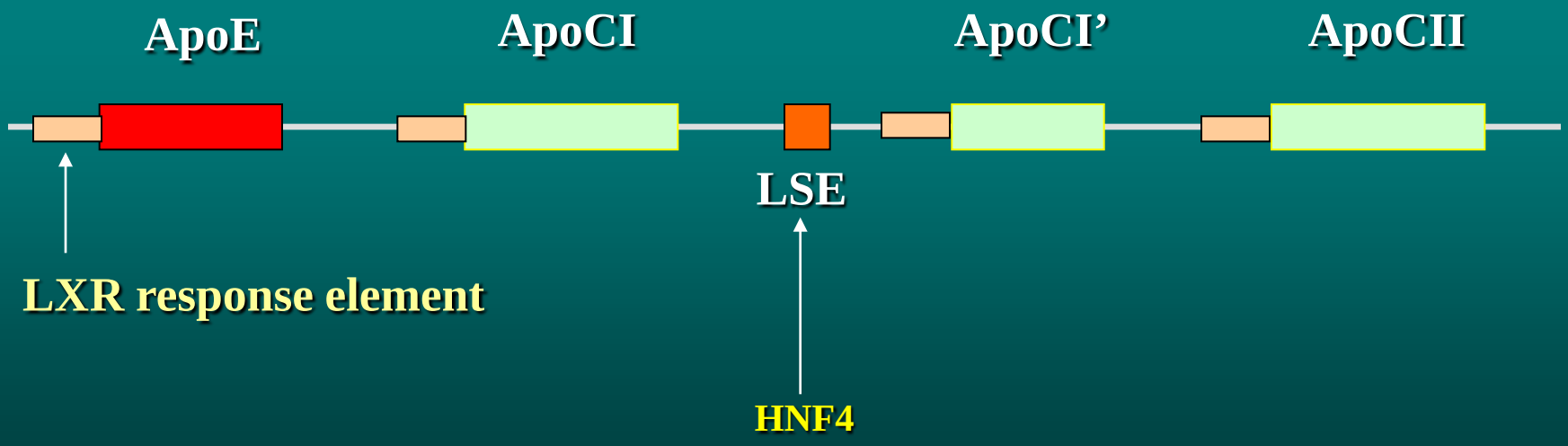
# Pharmacologic Manipulation of Cholesterol Efflux



# Target genes for LXR

* ApoE – protein responsible for clearens of VLDL, LDL, IDL and receiving cholesterol in reverse transportation.

* Regulation of apoE expression by LXR is tissue-specific. Consensus sequence is present in the promoter – its activation results in increased expression in adipocytes and macrophages, but it is not so important in hepatocytes. There the major regulator of expression is LSE (liver specific enhancer) located ~15 kb downstream.



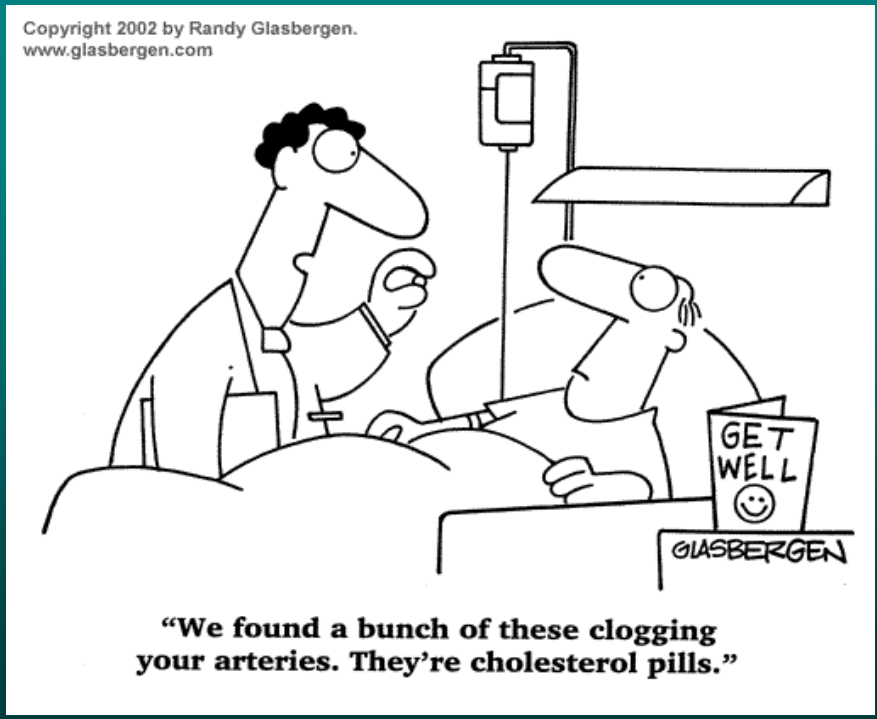
# LXR

- The **conversion of cholesterol to hydrophilic bile acids** in the liver is a major pathway for **its elimination** from the body.

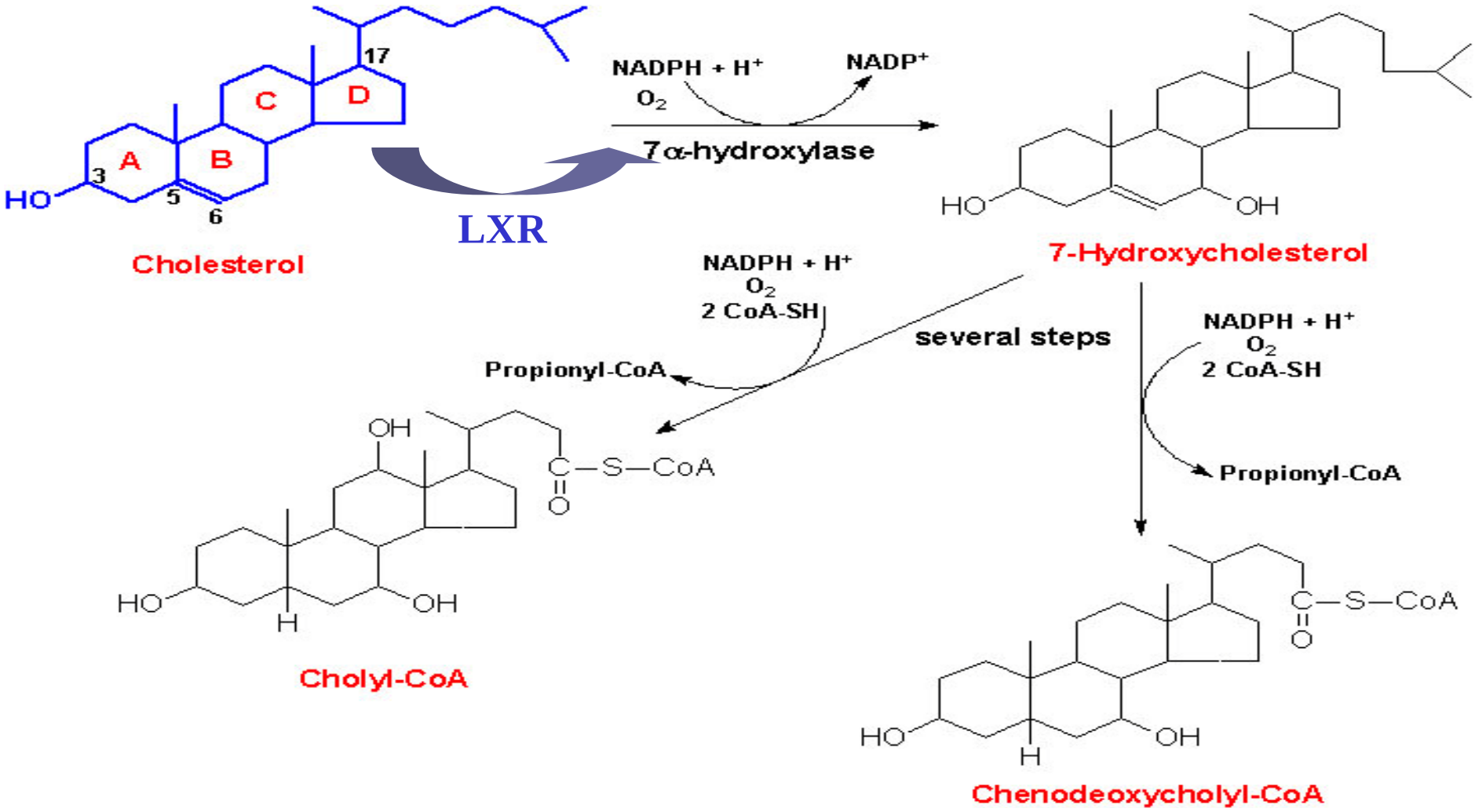
- Dietary cholesterol increases transcription of the **cholesterol 7a-hydroxylase (CYP7a)** gene, which encodes the enzyme responsible for the rate-limiting step in the conversion of cholesterol to bile acids. This feed-forward regulatory pathway ensures the catabolism of excess cholesterol.

- **LXRα** binds as a heterodimer with RXR to a DNA response element in the **CYP7α** gene promoter.

- Cholesterol does not activate LXRa directly. Instead, two **oxysterols,** 24(*S*),25-epoxycholesterol (generated in shunt pathway of the cholesterol biosynthesis) and 24(*S*)-hydroxycholesterol (direct metabolite of cholesterol), bind and **activate LXRa** at physiological concentrations. Hepatic amounts of both oxysterols increase in response to dietary cholesterol.

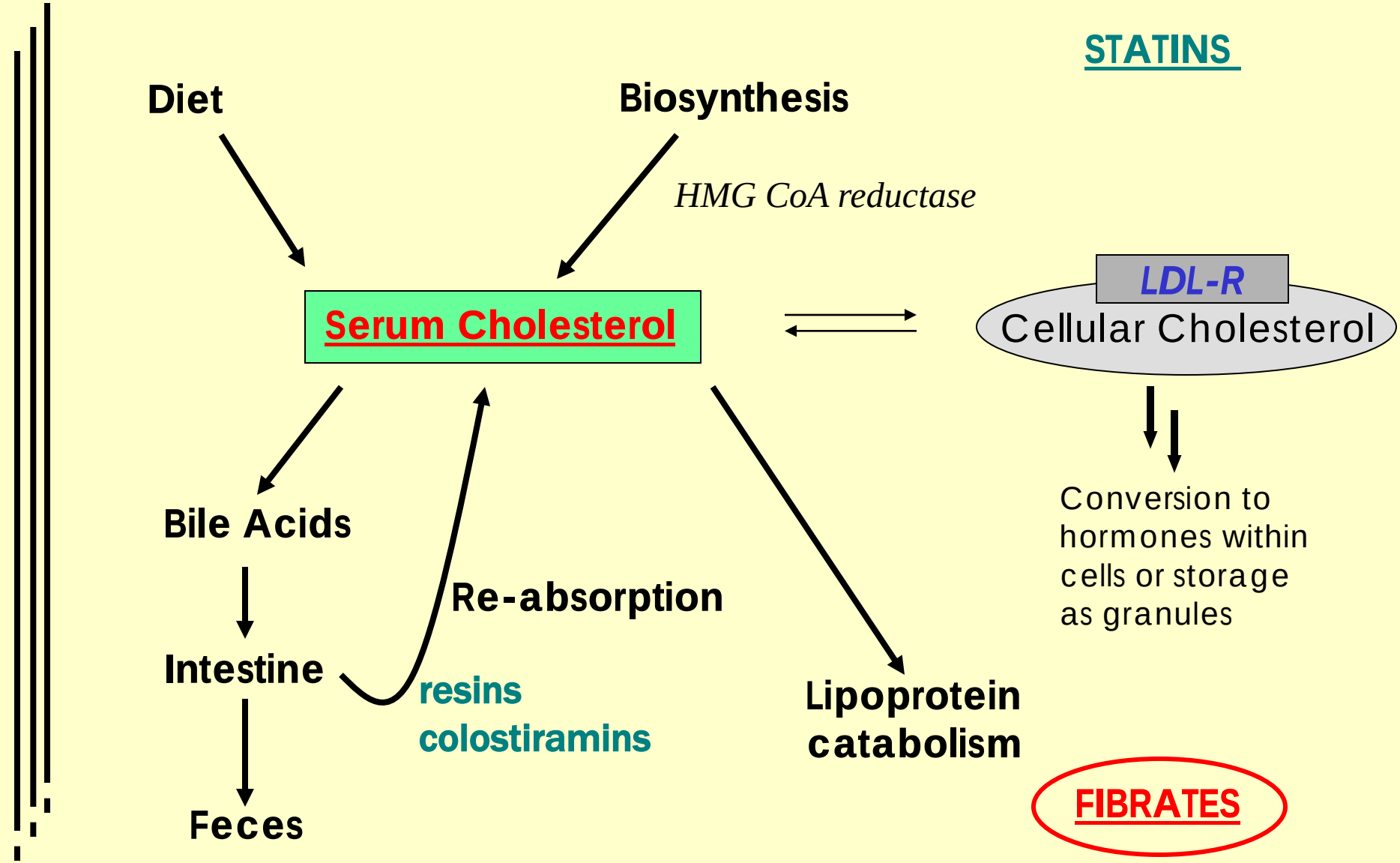


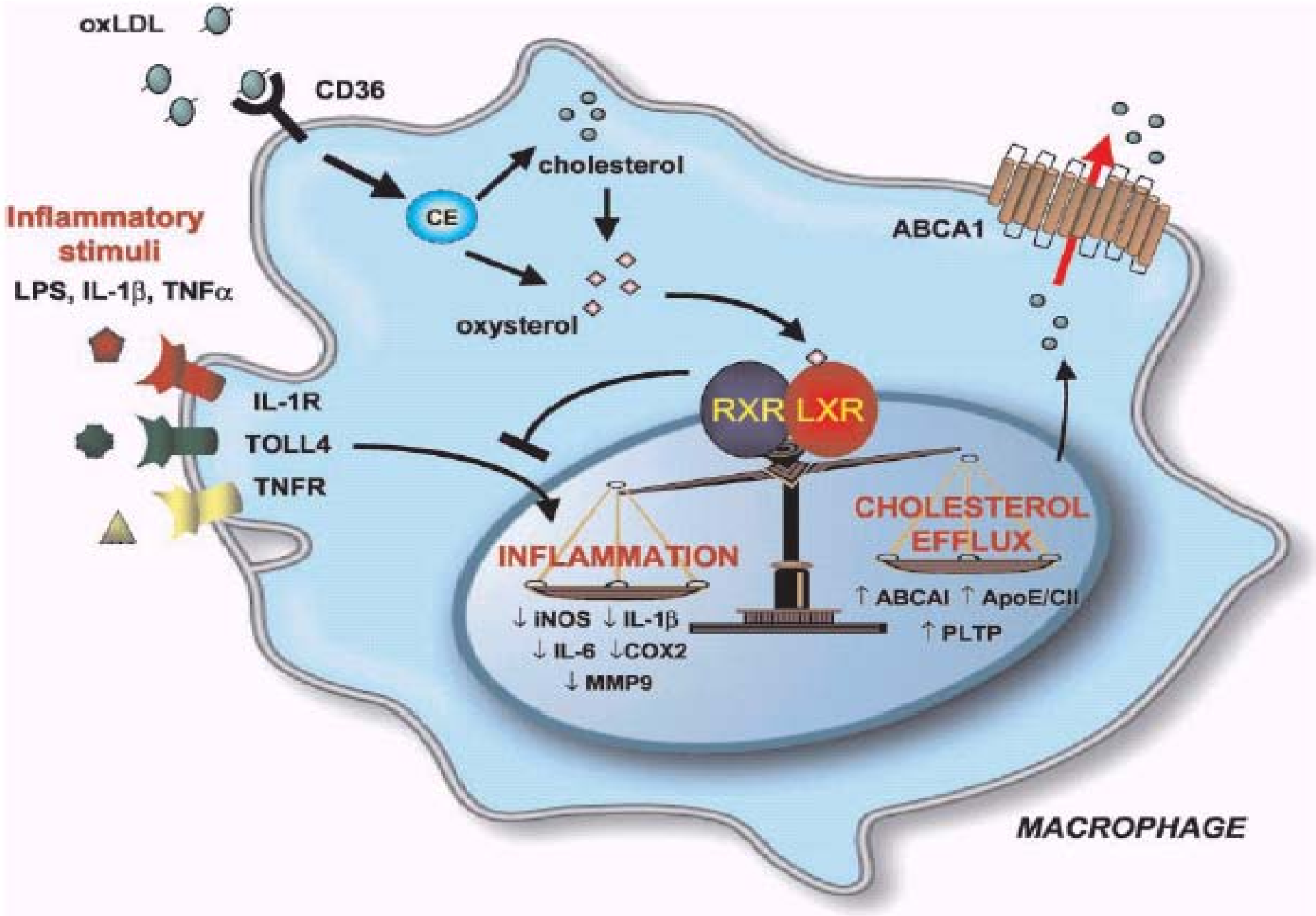
# The end products of cholesterol utilization are the bile acids in the liver



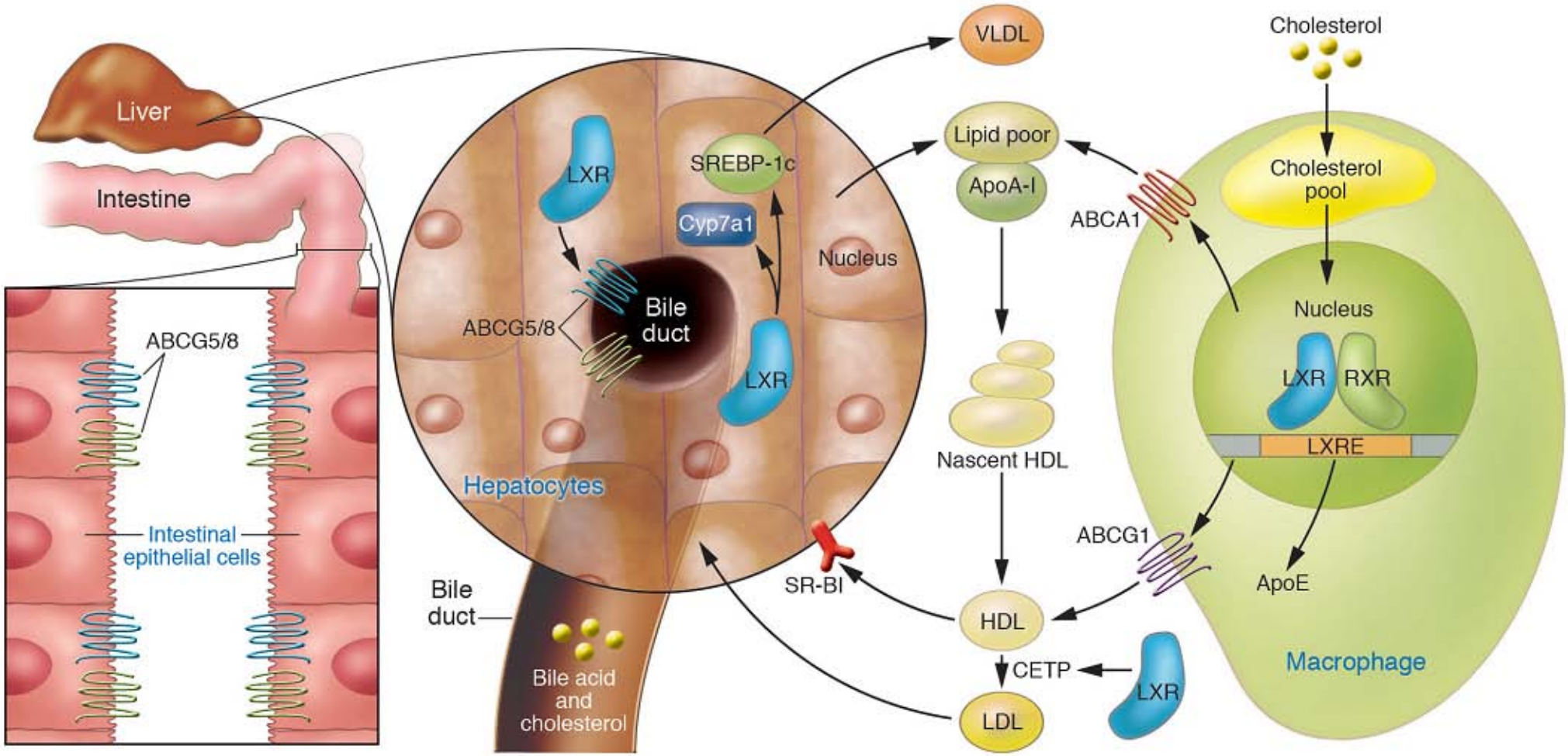

**Synthesis of the 2 primary bile acids, cholic acid and chenodeoxycholic acid (simplified). The reaction catalyzed by the 7α-hydroxylase is the rate limiting step in bile acid synthesis.**

# Strategy for Controlling Hyperlipidemia

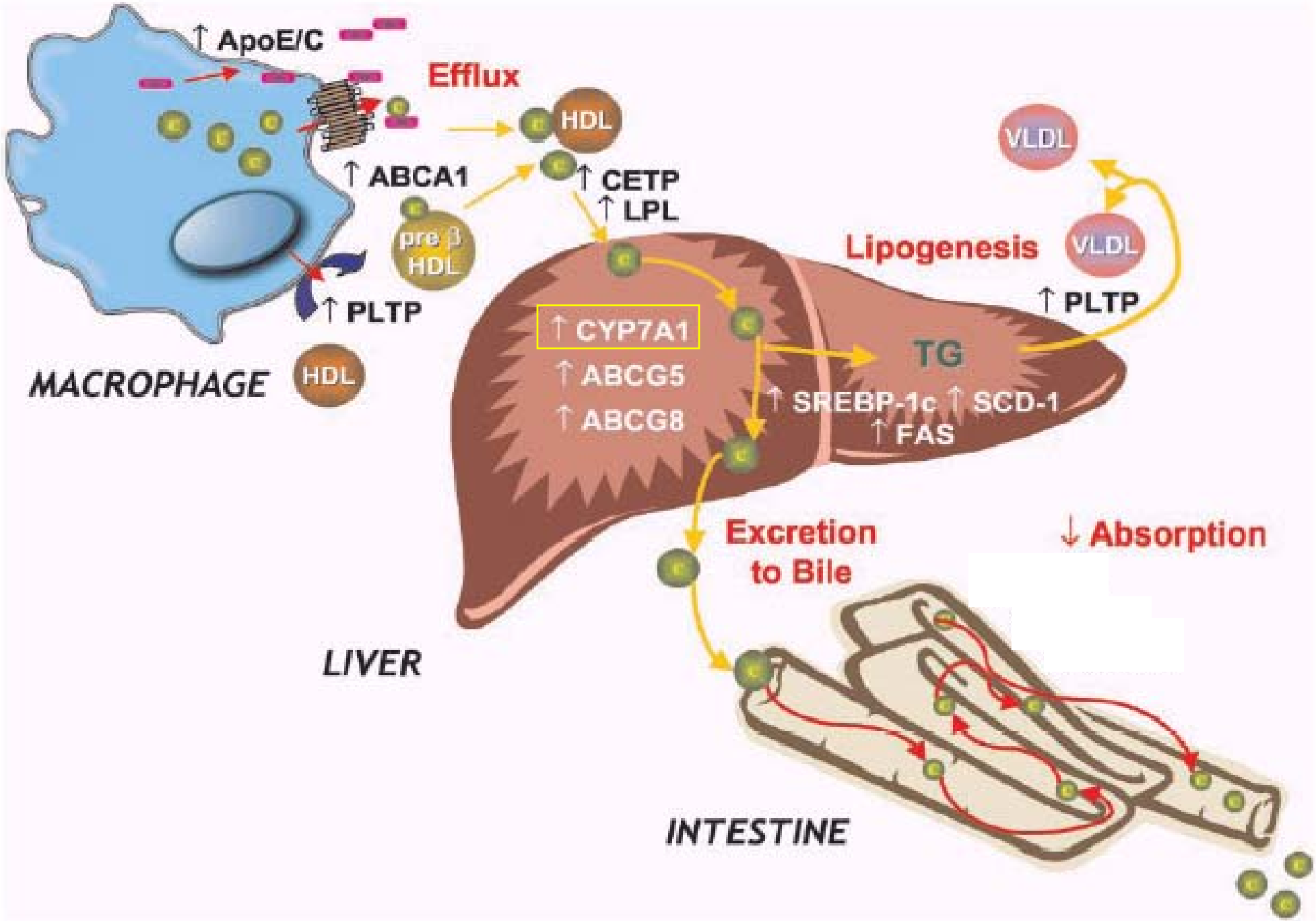



oxLDL
CD36
cholesterol
CE
oxysterol
ABCA1
Inflammatory stimuli
LPS, IL-1β, TNFα
IL-1R
TOLL4
TNFR
RXR LXR
INFLAMMATION
↓ iNOS ↓ IL-1β
↓ IL-6 ↓COX2
↓ MMP9
CHOLESTEROL EFFLUX
↑ ABCAI ↑ ApoE/CII
↑ PLTP
MACROPHAGE

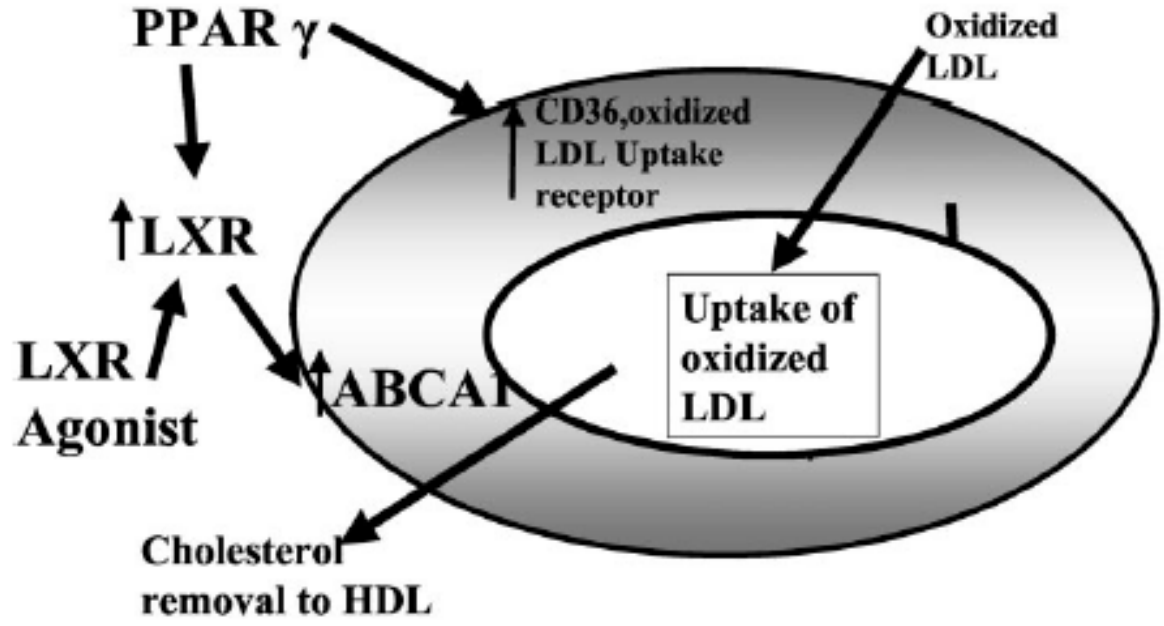
# LXR and cholesterol transport




Role of LXRs in reverse cholesterol transport from macrophages. The uptake of modified lipoproteins by macrophages results in increased LXR transcriptional activity and efflux of cholesterol to lipid-poor apoA-I by ABCA1 and to HDL by ABCG1. In humans, but not mice, induction of CETP expression transfers lipid from HDL to LDL. Once HDL/LDL is taken up by the liver, LXR promotes net cholesterol excretion. In rodents, but not humans, LXR induces expression of Cyp7a1, which initiates the conversion of cholesterol into bile acids. LXRs also induce cholesterol secretion into bile through the transporters ABCG5 and ABCG8. In the intestine, apical ABCG5 and ABCG8 also act to limit dietary cholesterol uptake.


↑ ApoE/C
Efflux
HDL
↑ ABCA1
↑ CETP
↑ LPL
pre β HDL
VLDL
Lipogenesis
VLDL
↑ PLTP
↑ PLTP
↑ CYP7A1
↑ ABCG5
↑ ABCG8
TG
↑ SREBP-1c ↑ SCD-1
↑ FAS
MACROPHAGE
HDL
Excretion to Bile
↓ Absorption
LIVER
INTESTINE

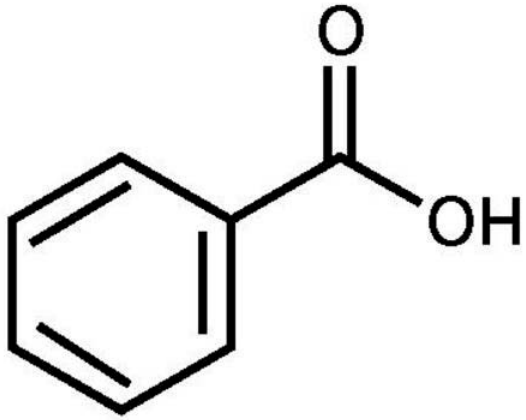
- **LXRs are activated by oxysterols and have a role in hepatic bile homeostasis.**
- **LXR stimulates transcription of the ATP-binding cassette 1 (ABCA1) transporter gene in the macrophage. This transporter removes cholesterol from foam cells, transferring it to HDL and thereby promoting reverse cholesterol transport to the liver.**
- **Thus, PPAR and LXR synergize in reverse cholesterol transport. For this reason, there is an intense effort to develop ligands that might be used to stimulate reverse cholesterol transport and remove cholesterol from arterial plaques.**
- **The LXRs and their ligands are also ligand-dependent inhibitors of inflammatory gene expression in macrophages and aortas of atherosclerotic mice, pointing to a dual and reciprocal role in lipid metabolism and inflammatory responses.**



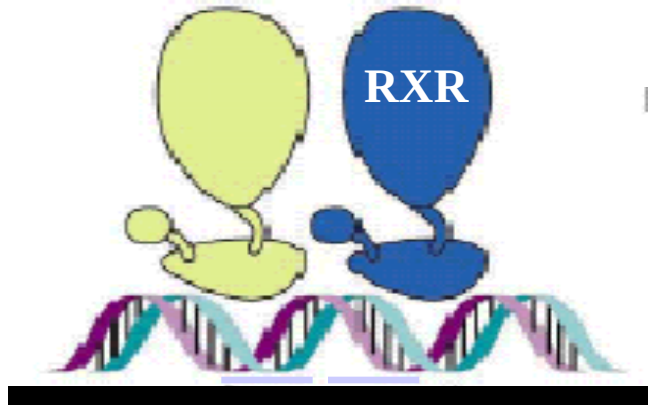

*PPAR enhances expression of CD36, which promotes uptake of oxidized LDL cholesterol into macrophages, and of LXR that induces expression of ABCA1, which enhances transport of cholesterol out of the cell.*

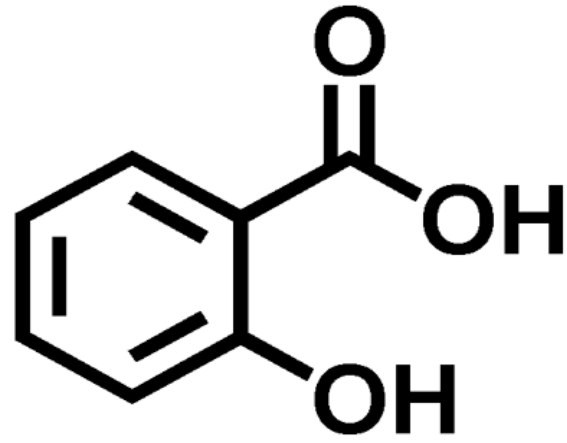
# Benzoate X Receptor (BXR) – adopted orphan receptor

- **BXR heterodimerizes with RXR and binds high-affinity DNA sites composed of a variant thyroid hormone response element.**
- **Recently, alkyl esters of amino and hydroxy benzoic acids were identified as potent, stereoselective activators. These molecules act as bona fide ligands.**
- **Benzoates comprise a new molecular class of nuclear receptor ligand and their activity suggests that BXR may control a previously unsuspected vertebrate signaling pathway.**
- **BXR:RXR heterodimers bind preferentially to direct repeats of the sequence AGTTCA separated by four nucleotides (DR4).**




**benzoic acid**

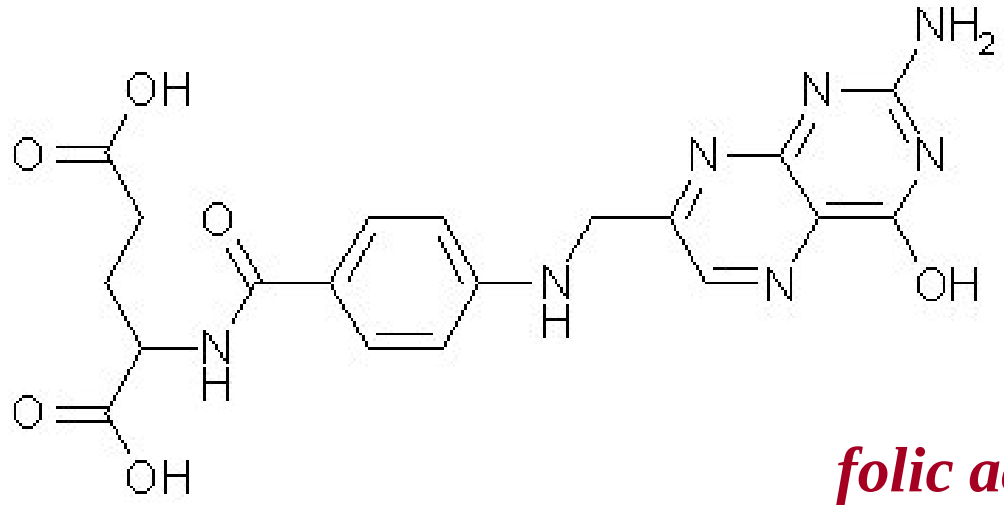



**salicylic acid**

# Benzoates

- **The endogenous benzoates are related to the nutrient *p*-amino benzoic acid (PABA), an integral component of the essential B-vitamin folic acid.**
- **Interestingly, folate lowers blood levels of homocysteine, which in high levels has been linked to heart disease and hypertension.**
- **This further suggests a connection between folate metabolism and BXR activation.**



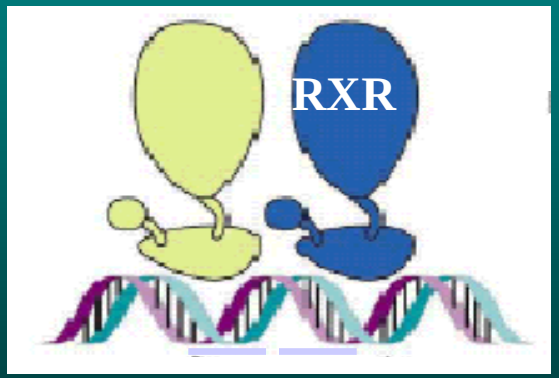

***folic acid***

# FXR (Farnesoid X Receptor)

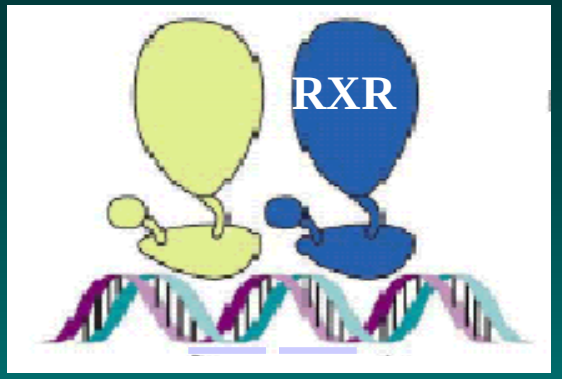
- FXR binds in a complex with RXR (activation of expression) or act as homodimer (inhibition of expression)
- FXR can be activated by high concentrations of farnesol. Farnesol is an isoprene intermediate in the mevalonate biosynthetic pathway and most likely activates FXR via its conversion into a higher affinity derivative.
- FXR was shown to be a receptor for bile acids (higher affinity than for farnesol).
- FXR is a general regulator of bile acid metabolism, acting through suppression of CYP7A to reduce synthesis.

# Pregnane X Receptor (PXR)

- PXR is predominantly expressed in the liver and intestine and is most closely related to the VDR at the structural and amino acid sequence levels.
- PXR recognize DR-3 motif as a heterodimer with RXR, and is responsible for the activation of the CYP3A4, CYP3A3, CYP3A23 and cholesterol 7a hydroxylase promoters.
- Naturally occurring steroids have been identified that are efficacious activators of PXR. The most potent compounds are C21 steroids (pregnanes) such as the progesterone metabolite 5b-pregnane-3,20-dione, but corticosteroids and estrogens also activate PXR.
- Thus, in addition to serving as a xenobiotic sensor, PXR is also likely to have important implications in the regulation of steroid homeostasis.
- In patients on steroid replacement therapy, or women taking oral contraceptives, activation of PXR leads to rapid depletion of administered steroids.
- PXR induces multidrug resistance gene MDR-1 (important in drug resistancy in treatment of tumors) and inducible nitric oxide synthase iNOS (induction of inflammation and contribution to septic shock).



# Steroid X Receptor (SXR)



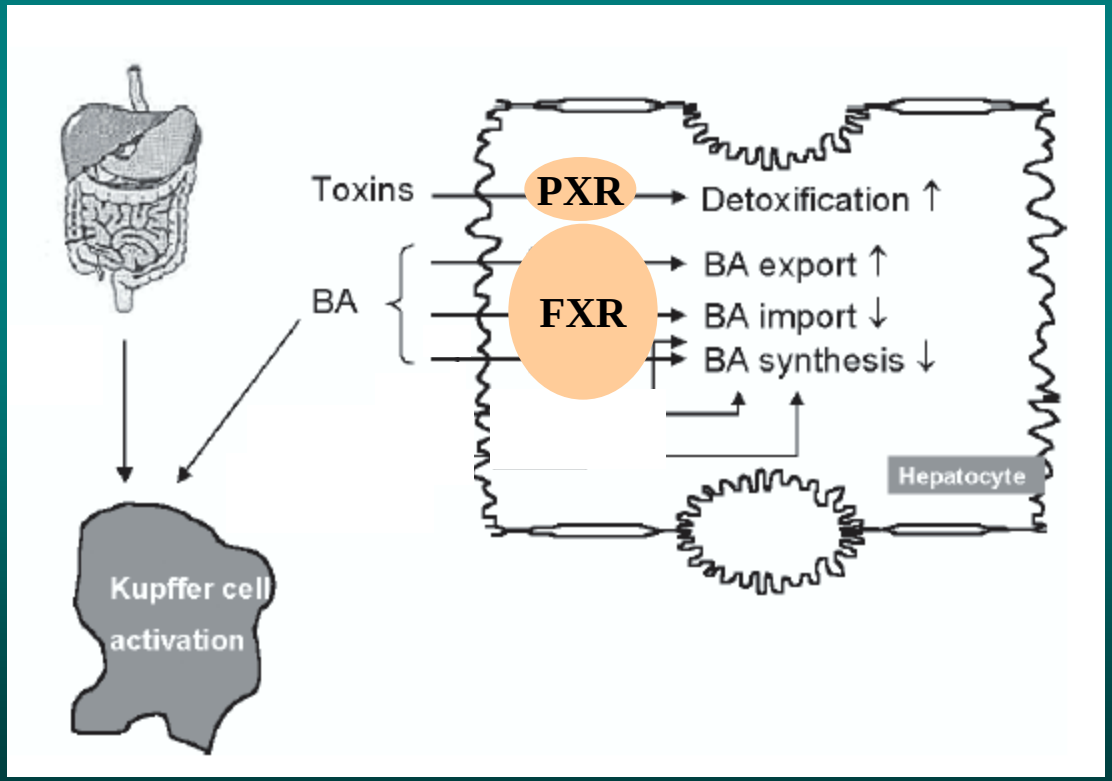

- Although related to both BXR and PXR this receptor is pharmacologically distinct
- SXR receptor was shown to be activated by a diverse group of steroid agonists and antagonists including estranes, androstanes, and pregnanes (C18, C19, and C21 steroids, respectively).
- The response profile of SXR led to a novel model, 'the steroid sensor hypothesis,' which proposes that the detoxification and removal of various endogenous hormones, dietary steroids, drugs, and xenobiotic compounds with biological activity are regulated through the activation of a few broad-specificity sensing receptors rather than by numerous, specific receptors.
- Much of the detoxification and catabolism of such compounds is mediated by cytochrome P450 enzymes, particularly members of the CYP2A, CYP2B, CYP2C, CYP2D, CYP2E, and CYP3A families, most of which have broad substrate specificity and are inducible by a diversity of compounds, including steroids

# Detoxification

• The efficient detoxification of harmful xenobiotics is essential to the survival of all organisms. Members of the cytochrome P450 (CYP) superfamily of monooxygenases are crucial for the detoxification of most xenobiotics, including various environmental pollutants, carcinogens, and drugs.

• The CYPs are also responsible for the oxidative metabolism of endogenous compounds, including many steroid hormones.

• The **CYP3A4 isozyme** is of particular significance from a medical perspective because it is involved in the **metabolism of roughly 50% of all drugs**, including antibiotics, antimycotics, glucocorticoids, statins, tamoxifen, and phytoestrogens.



# TLX – Tailless orphan receptor

• Tlx is a member of the *tailless* class of orphan nuclear receptors, a highly conserved family in both vertebrates and invertebrates.

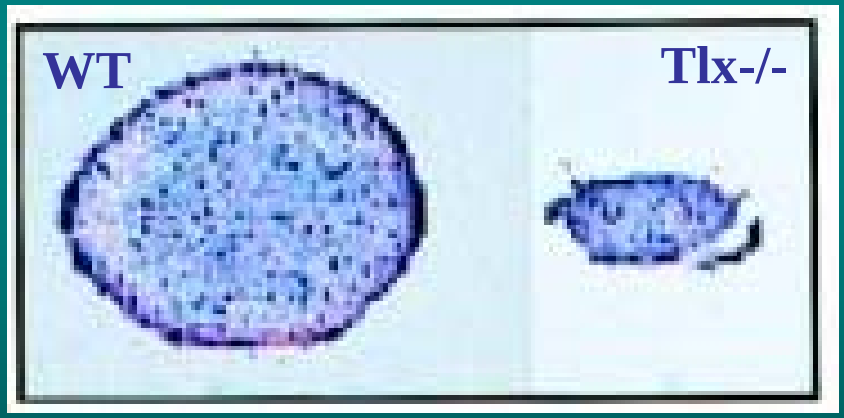
• The evolutionary conservation of the pattern of Tlx expression in the embryonic forebrain, midbrain, and optic vesicle in vertebrates suggested that Tlx may participate in the formation of central nervous system-derived structures.

• Orphan receptor that binds DNA as a monomer.

• In mice it is required to brain differentiation.

• Involved in the regulation of retinal development and essential for vision.

• $TLX^{-/-}$ mice show:




*Section through optic nerves*

* central nervous system cortical defects
* progressive retinal and optic nerve degradation with associated blindness.

# TLX – Tailless orphan receptor

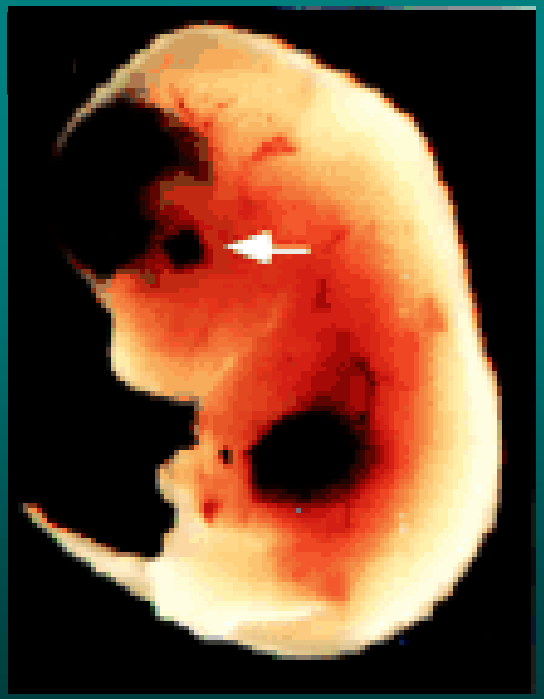
- TLX was initially identified as an orphan nuclear receptor expressed in vertebrate forebrains and is highly expressed in the adult brain.

- The brains of TLX-null mice have been reported to have no obvious defects during embryogenesis; however, mature mice suffer from retinopathies, reduced copulation and progressively violent behaviour.

- The finding of neurogenesis in the adult brain led to the discovery of adult neural stem cells

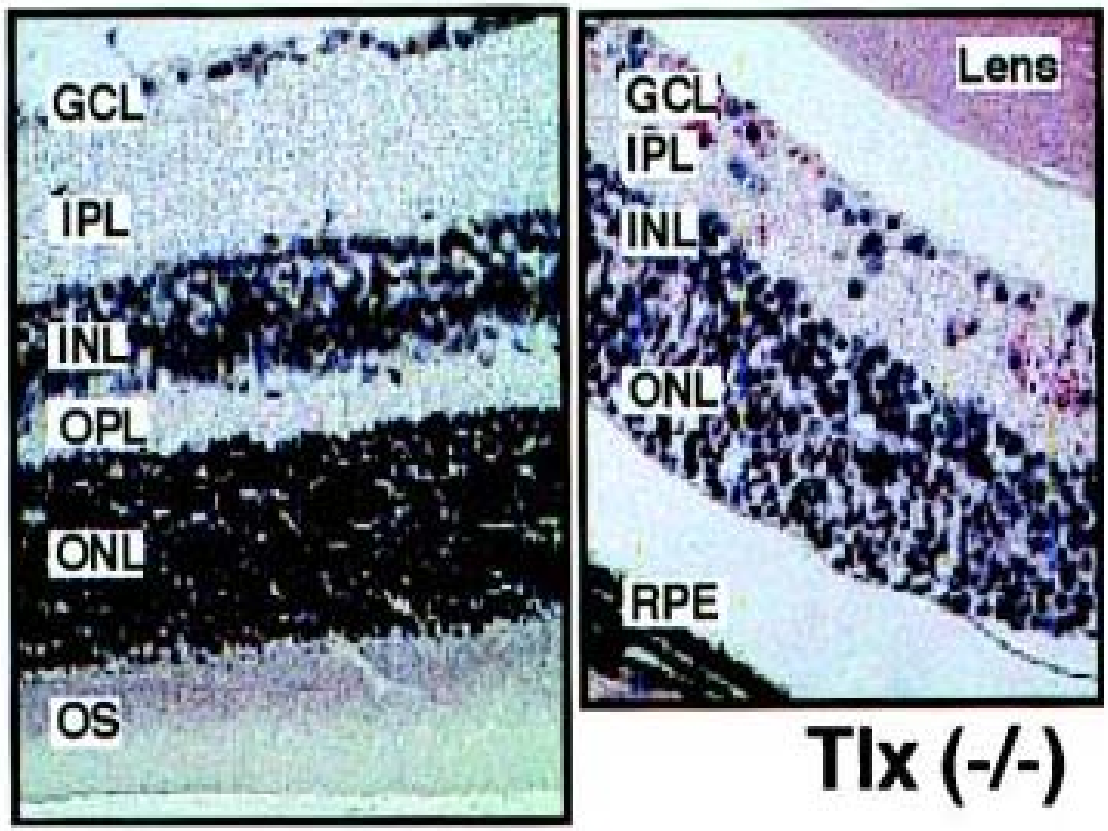
- TLX maintains adult neural stem cells in an undifferentiated, proliferative state. TLX-expressing cells from adult brains can proliferate, self-renew and differentiate into all neural cell types *in vitro*. By contrast, TLX-null cells from adult mutant brains fail to proliferate.

- Thus, TLX plays a role in adult neurogenesis.



# TLX

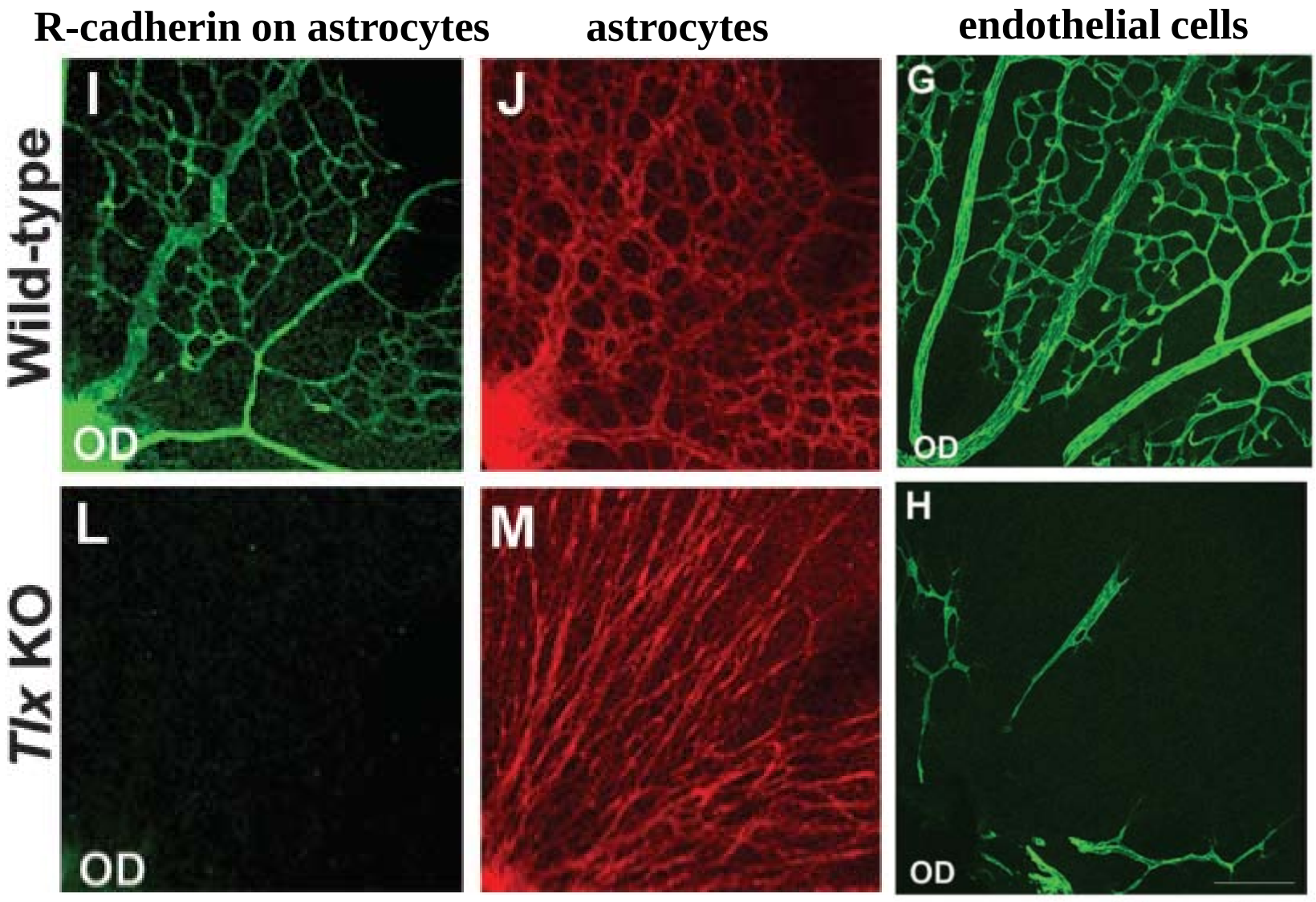
- **In neural precursors the target gene for TLX is Pax2, a protein involved in retinal development.**
- **Tlx is a key component of retinal development and vision acting as an upstream regulator of the Pax2 signaling cascade.**




Histological sections through the eye of a WT and Tlx−/− mouse showing disorganization of the ganglion cell layer (GCL) and the inner (INL) and outer nuclear layers (ONL) as well as absence of outer plexiform and outer segment layers.

IPL, inner plexiform layer;
OPL, outer plexiform layer;
OS, outer segments;
RPE, retinal pigmented epithelium.

# Morphogenetic defects in network formation of *Tlx* KO mice

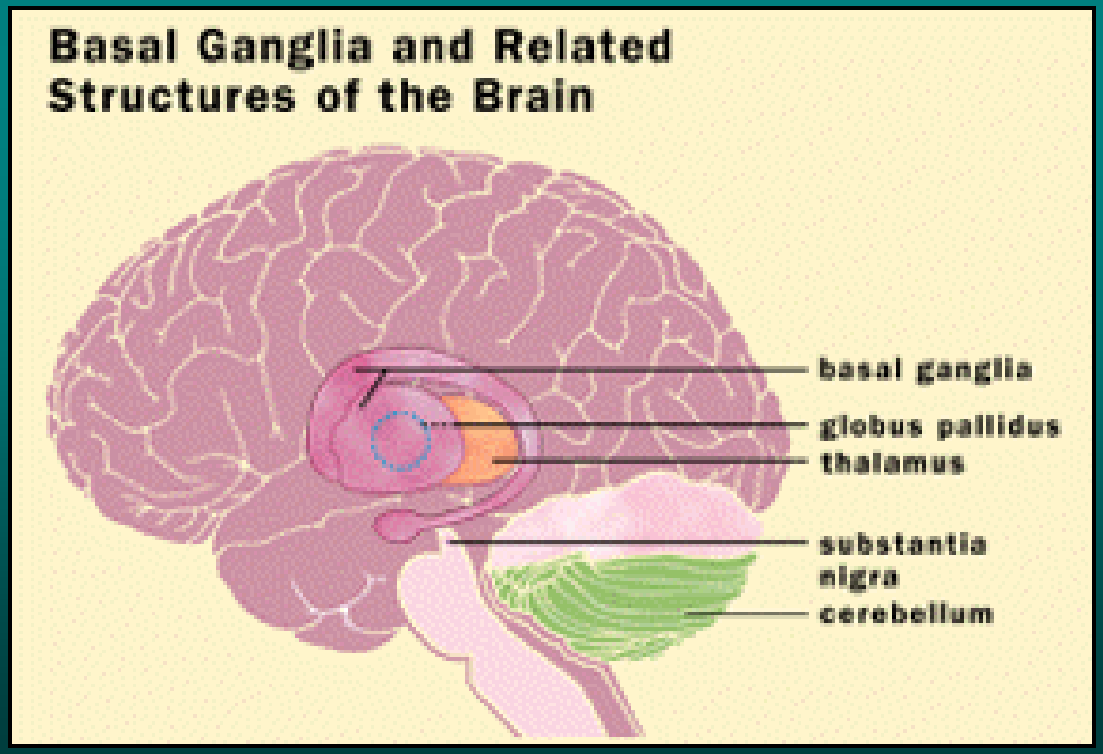


# Parkinson's Desease - Background Facts

- Degeneration of the dopaminergic neurones of the substantia nigra

- At diagnosis 50% of dopaminergic neurons are dead, and the surviving neurones are under-performing

- Striatal dopamine reduced by 80%.



# Parkinson's disease (PD)

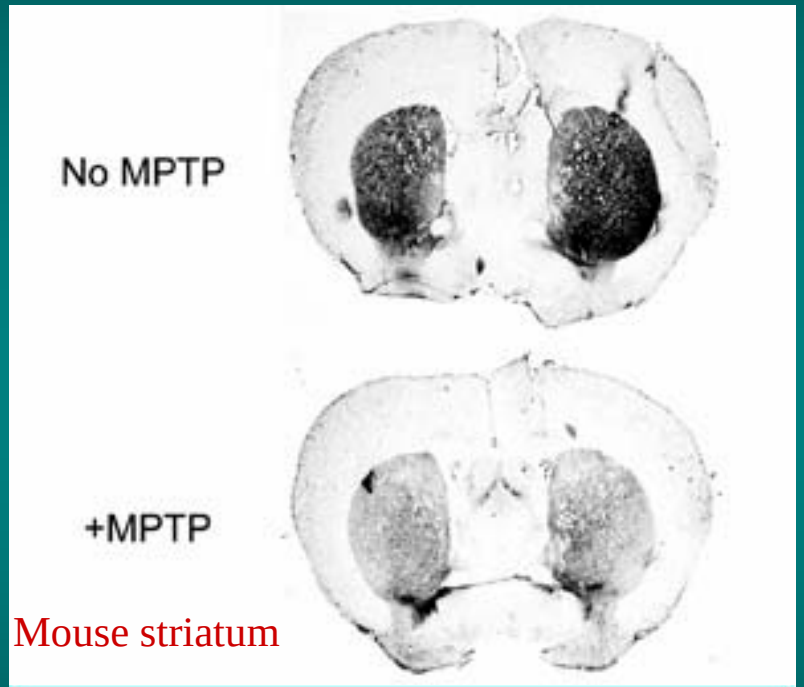
- Second in frequency neurogenerative disease in Europe, whose symptoms are among others the handicap of movements and muscle trembling.

- Results from progressive and selective lost of dopaminergic neurons, especially in substantia nigra.

- More often in men than in women.

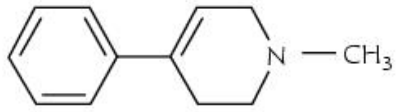
- In the early phase supplementation with L-DOPA is helpful, but in most patients after some time it becomes ineffectve, or there are fluctuation of higher and lower sensitivity.

- An **animal model of PD are MPTP-treated monkeys or mice** (1-methyl-4-phenylpyridinium ion, MPP+, Induces selective lost of dopaminergic neurons). Effects are weaker in females and reduced by 17β-estratiol.

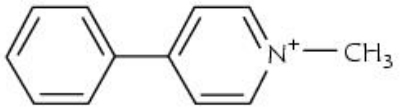


Mouse striatum

MPTP

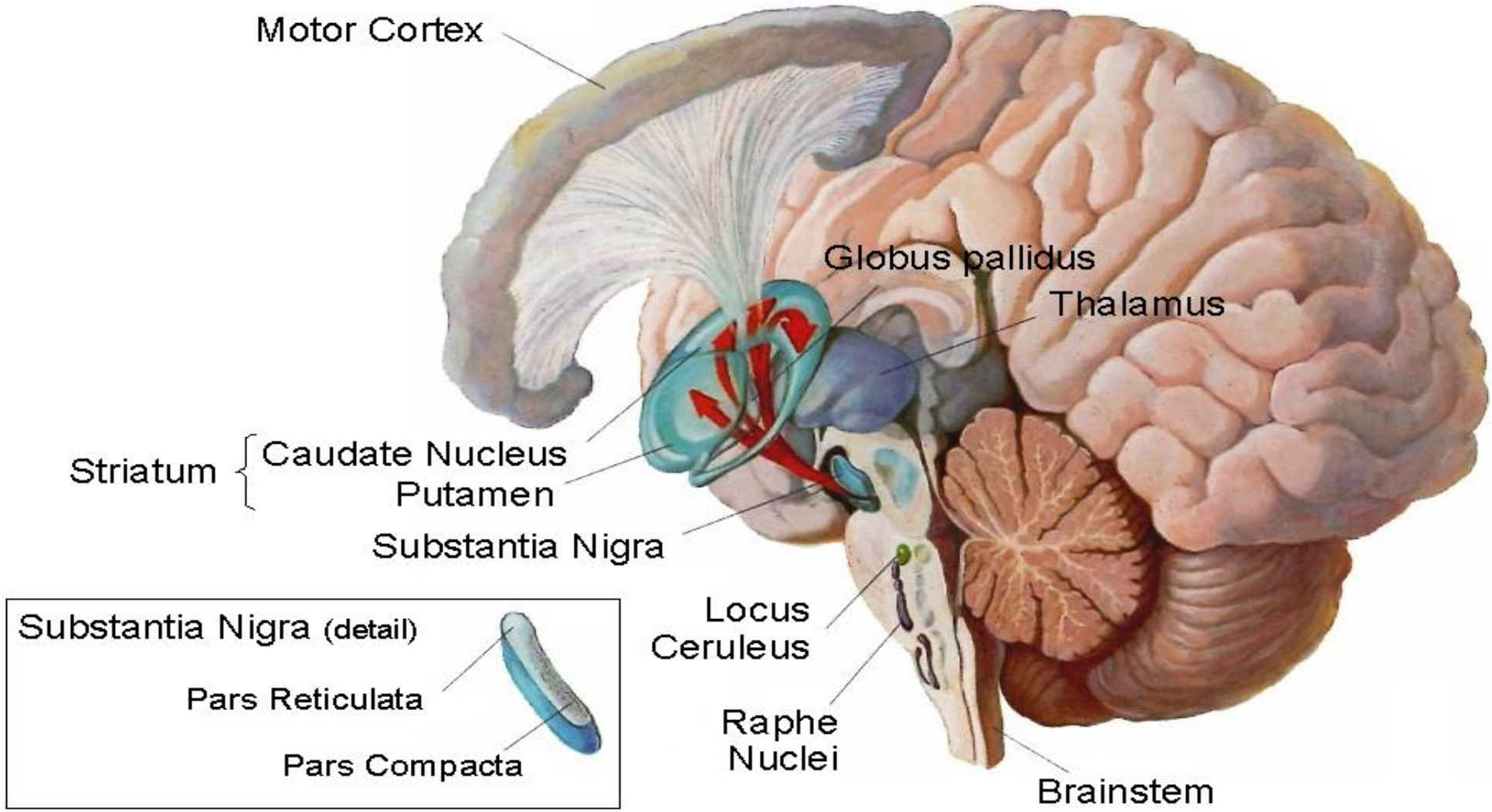



MPP



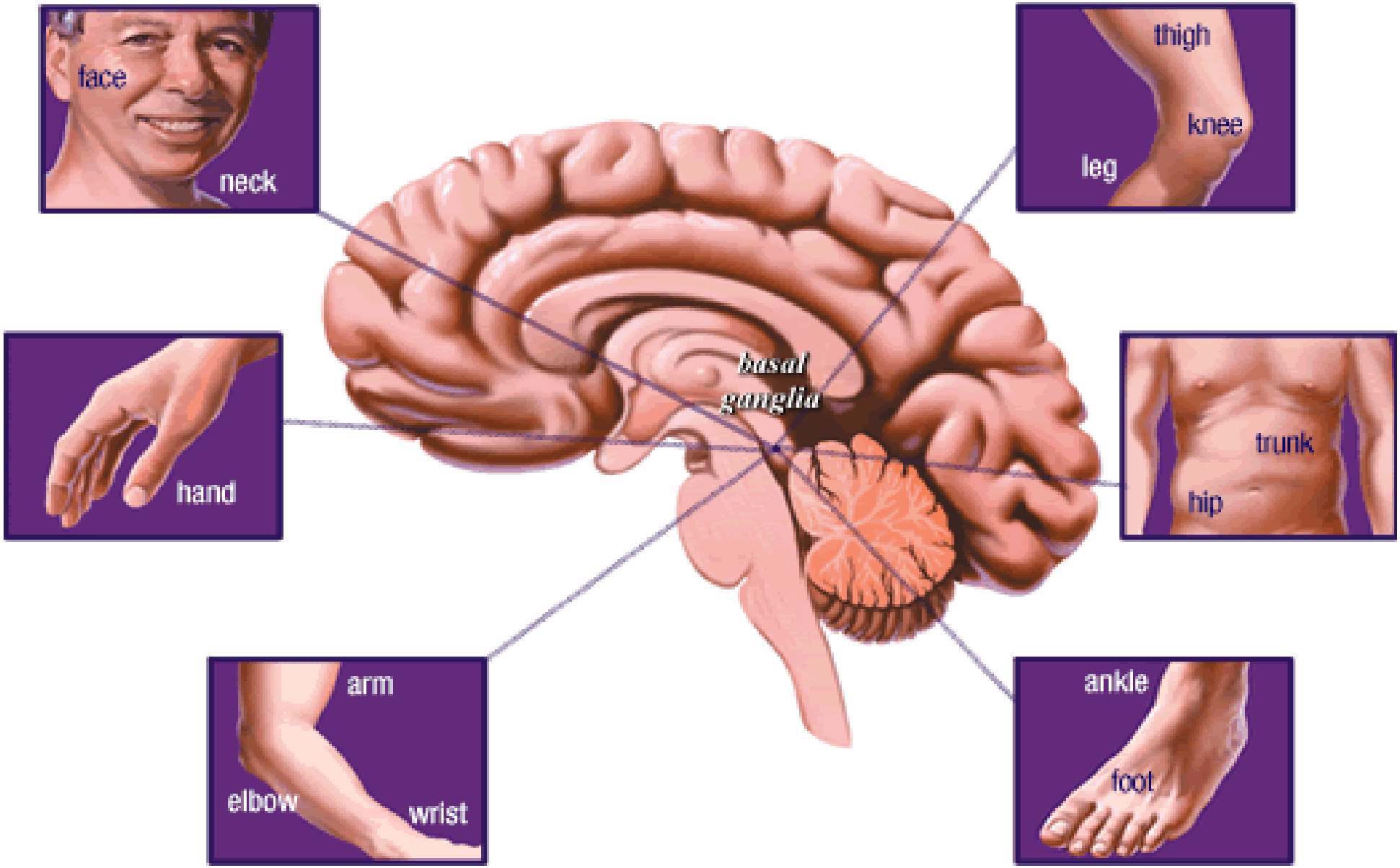
**So-called frozen addicts** posed together in 1991, after having received treatment. Nine years earlier all suddenly became immobile, as if they had instantly acquired Parkinson's disease, after taking heroin containing an impurity, MPTP. Studies of how MPTP led to the freezing has generated many insights into the biochemical reactions that could contribute to a more classical presentation of the disease,

# Brain Regions Affected by Parkinson's Disease

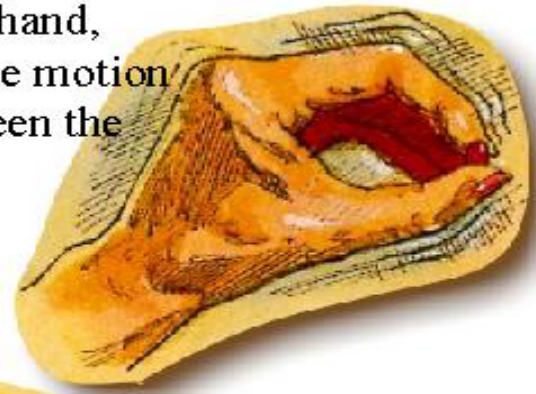



Parkinson's disease

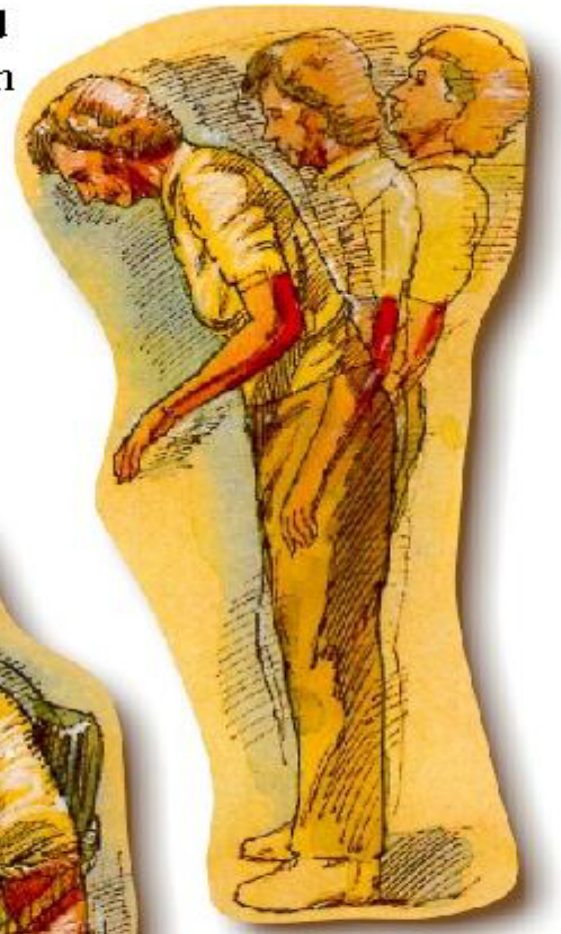
# Nerve cells in the basal ganglia send messages that signal the body to move



**Rhythmic tremor** often occurs at first in one hand, where it resembles the motion of rolling a pill between the thumb and forefinger



**Leaning forward** or backward when upright reflects impairment of balance and coordination.

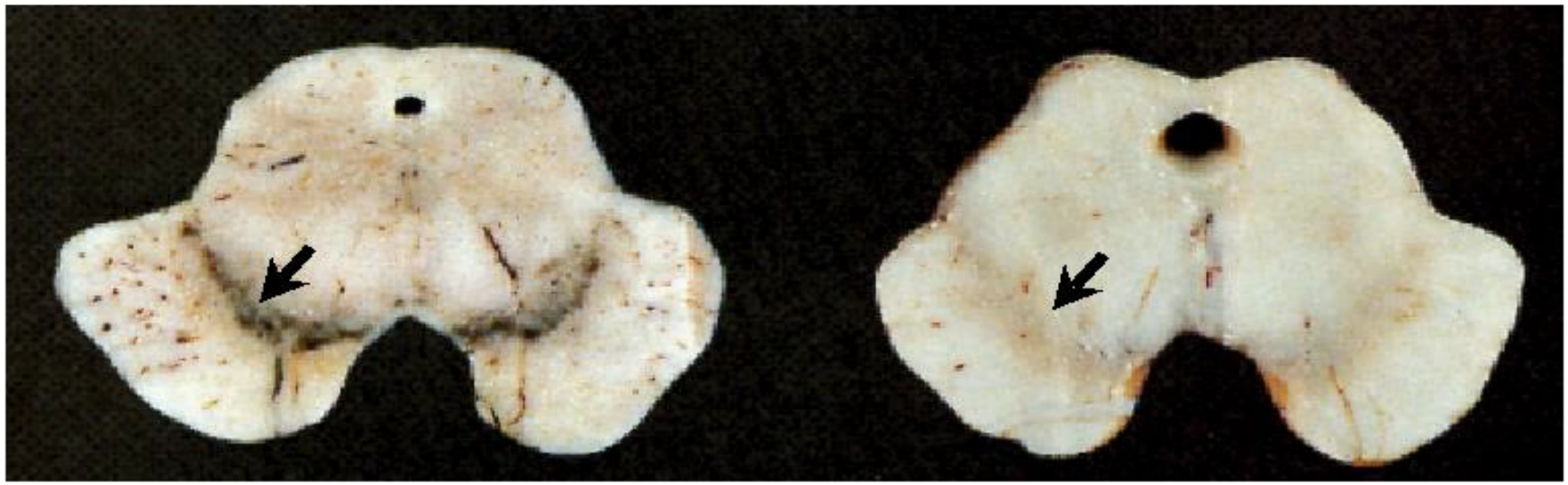


**Muscle rigidity** shows itself in the cogwheel phenomenon: pushing on an arm causes it to move in jerky increments instead of smoothly.

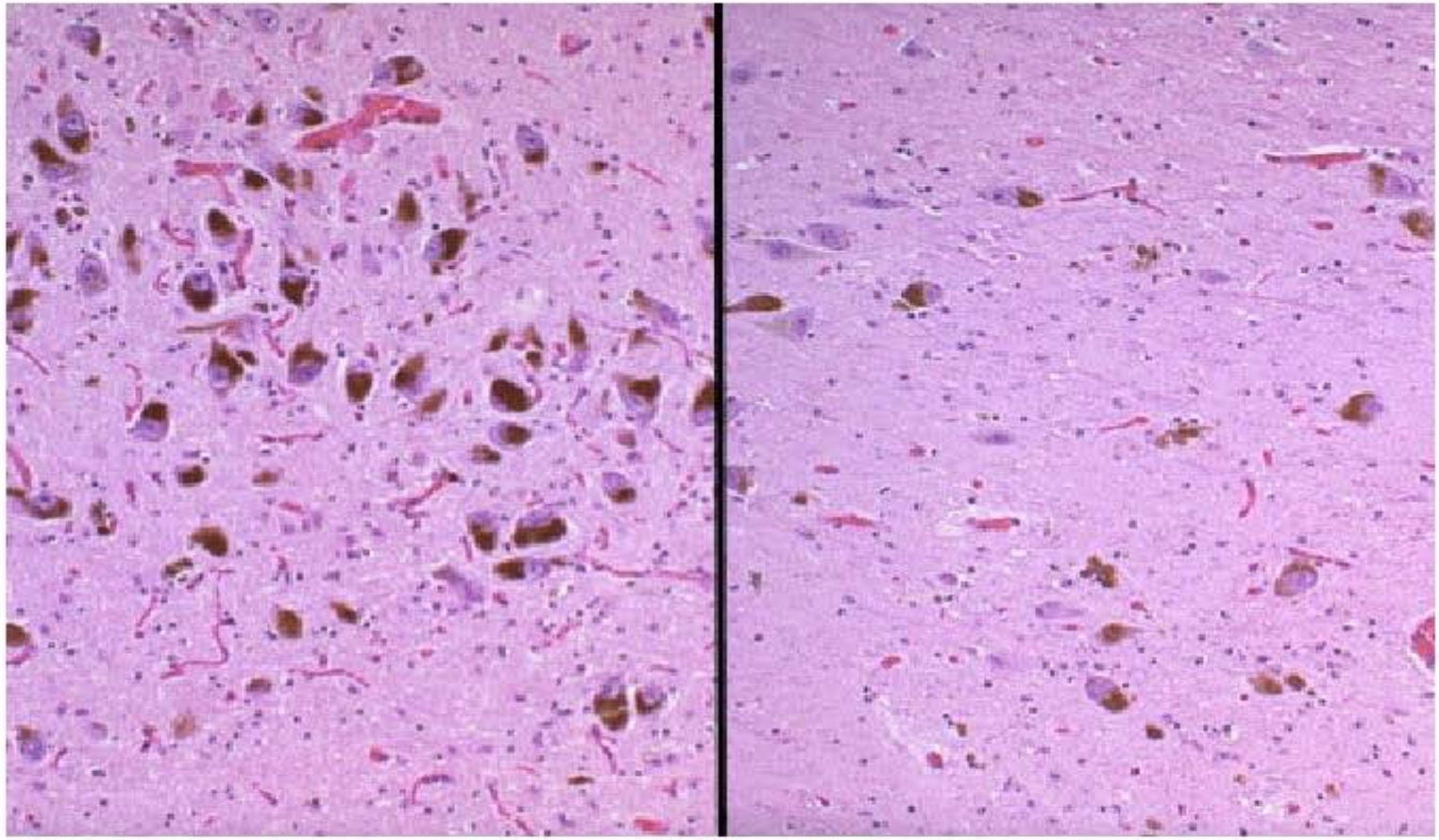
**Difficulty rising** from a sitting position is a common sign of disordered control over movement. Some patients report feelings of weakness and of being constrained by ropes or other forces.

Parkinson's disease

Normal Parkinson's



The pars compacta region of the substantia nigra in the normal brain appears dark because dopamine-producing neurons are highly pigmented; as neurons die from Parkinson's disease, the color fades.



At the left, normal numbers of neurons in the subtantia nigra are pigmented. At the right, there is loss of neurons and loss of pigmentation with Parkinson's disease.

# Parkinson's disease – neuron transplantation

- Some reports demonstrate that brain damage resulting from selective lost of substantia nigra may be reversed by transplantation of embryonal neurons.

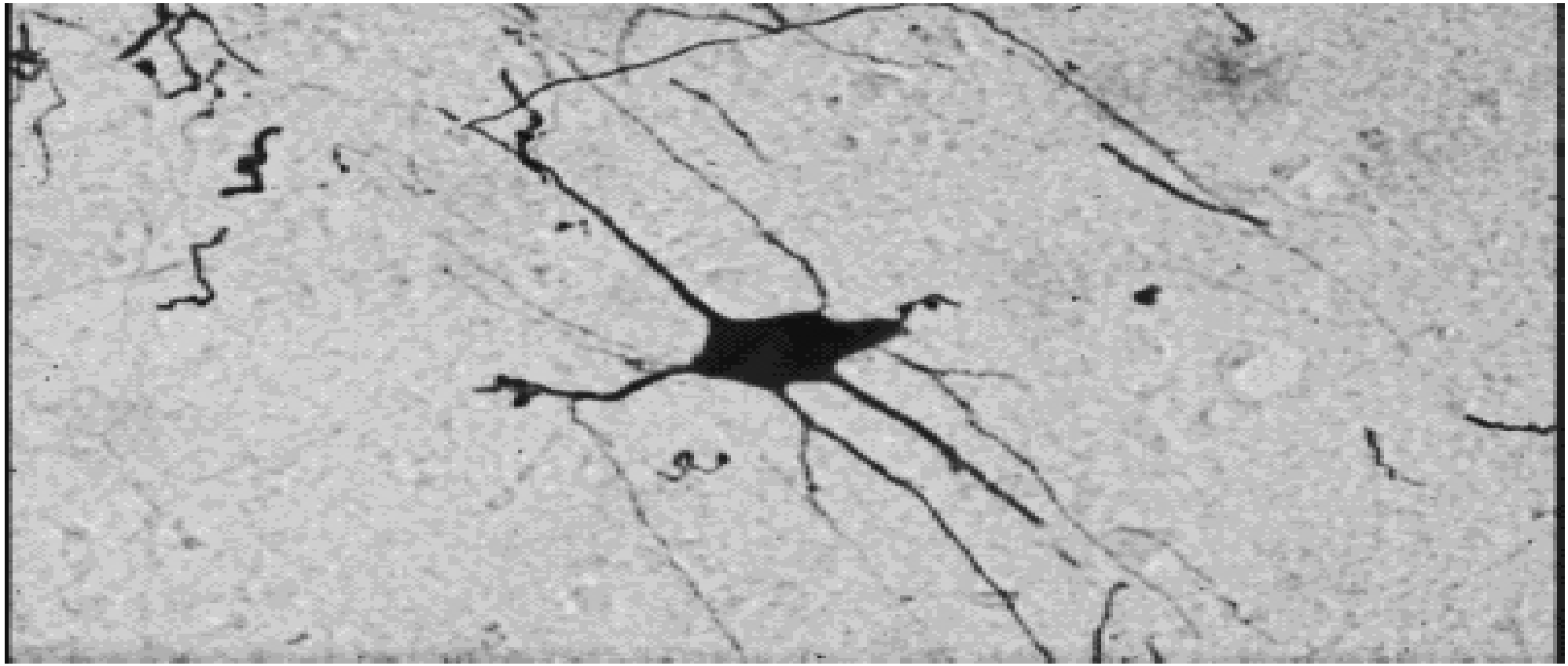
- Cells transplanted to striatum survive and start to function, what leads to restoration of striatum innervation and clinical improvement. Data are not univocal, but in the most successful cases patients could resign from L-DOPA. The bigest problem is an access to the embryonal tissues.

- Current methods allow for surviving only 5-20% of neurons. This means that tissue from 3-4 embryos are required for clinical improvements of one patients. In animal studies the survival rate could be increased by antioxidants, trophic substances and caspase inhibitors.

- Another solution can be xenotransplantation. Attemps of transplantation of embryonal pig neurons were, however unsuccessful – neurone survival rate was weak and clinical output not clear.

- There were attemps to transplant of dopaminergic neurons from other sites (e.g. adrenal cortex) – but survival rate was very low, while clinical output was very weak and short-lasting.

Human fetal dopamine neuron in putamen of Parkinson's patient dying 8 years after cell transplantation. The cell is immunostained for tyrosine hydroxylase and has multiple processes growing out from the cell body to specifically reinnervate the surrounding brain region. Other staining methods used on other transplanted cells in the same patient revealed the neuromelanin pigment particles typical of mature substantia nigra dopamine neurons. Immunosuppression was used for the first year after transplant, but not for the subsequent 7 years. If human ES cells can be differentiated to a phenotype identical to fetal substantia nigra dopamine neurons, those cells should have the same stable survival seen in this patient's transplant. (Magnification: ×400.)



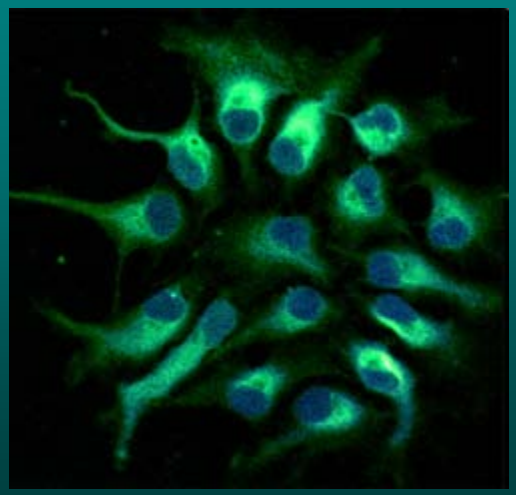
*Freed et al. Neurosurg Focus, 2002.*

# Parkinson’s disease – neuron transplantation

- In the begining of 1990s genetic modification (overexpression of tyrosine hydroxylase cDNA) was proposed to increase dopamine production, but it was difficult to obtain a stable and strong expression.

- Maybe the best solution would be to establish a method for in vitro propagation and differentiation of neuronal progenitor cells for transplantation.

- Differentiation of neuronal progenitors to dopaminergic cells significantly facilitated by overexpression of Nurr-1 nuclear receptor.



# Nurr-1

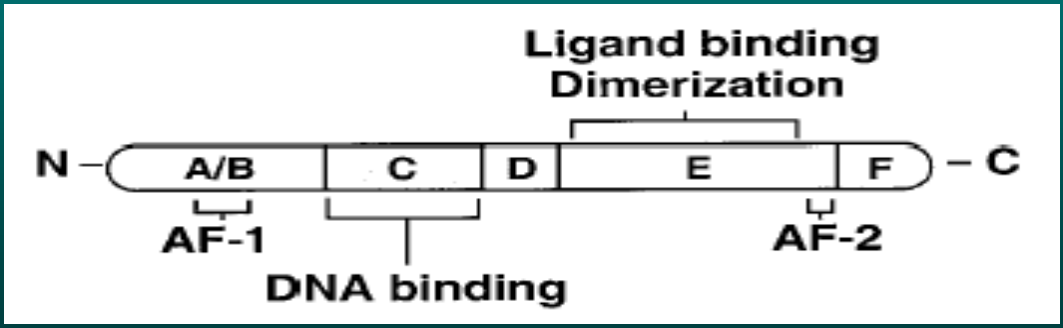
- Nurr-1 is an orphan receptor characterized in 1992.

- There are 3 known proteins of this family: Nurr77 (NGFI-B), Nurr-1 i Nor1

- Its expression is found mostly in the brain, specifically in dopaminergic neurons.

- Its expression can be strongly induced e.g. by trophic factors or ischemia.

- Nurr1 knockout mice have strongly disturbed development of neurons, especially dopaminergic neurons in the midbrain (but maybe have normal dopaminergic innervation e.g. in the olfactory bulb). Puppies cannot thrive and die several hours after birth).




598 aminoacids
66 kDa
8 exons
2 splicing forms

# Nurr-1

- Act as monomeric transcription factor binding to AAAGGTCA sequence

- As monomer Nurr-1 leads to stable expression of target genes. For its activation both AF1 and AF2 domains are important.

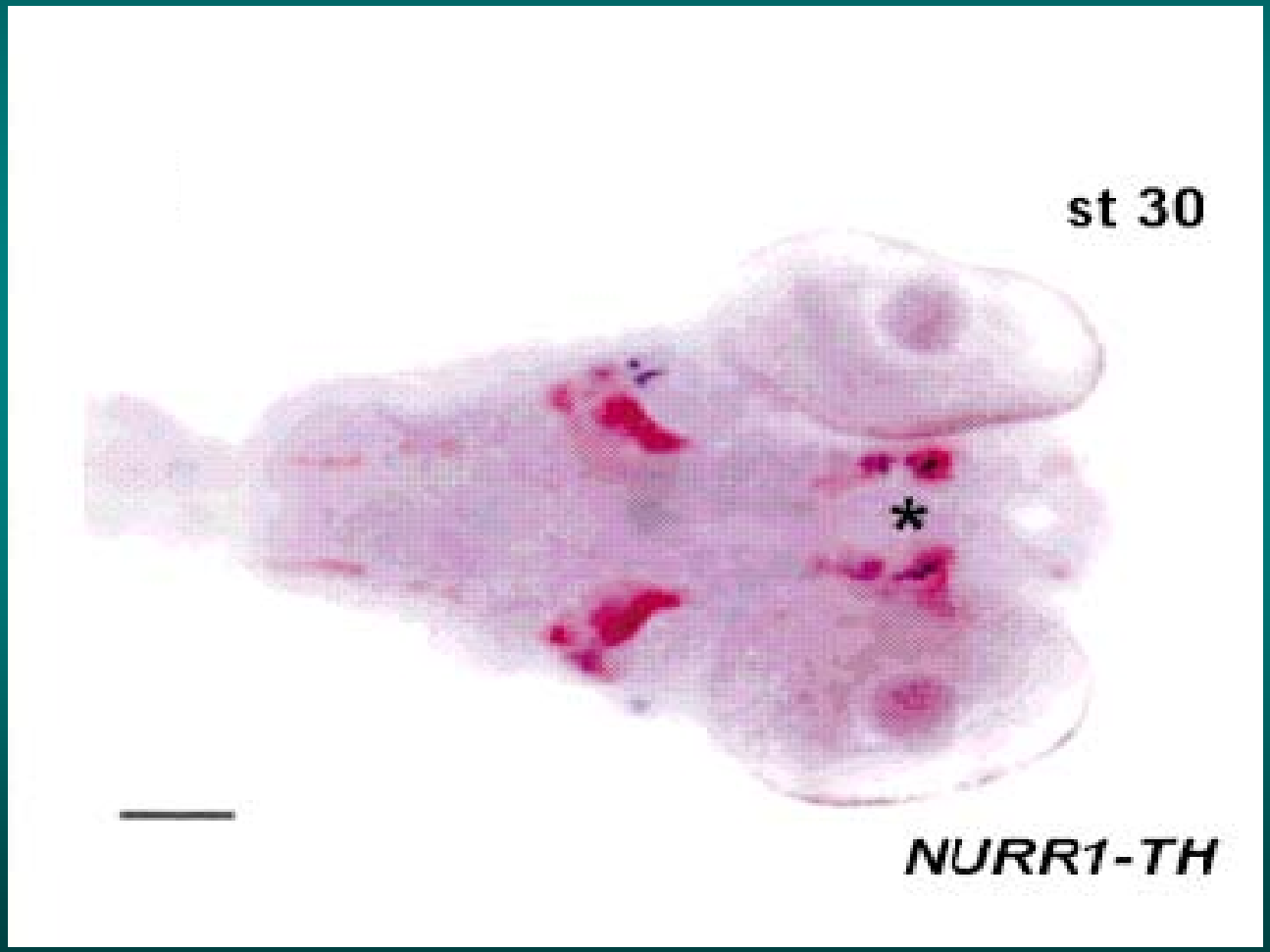
- In some cases it acts as a permissive heterodimer with RXR. In this case a comples recognizes DR5 sequence.

- In some cases it can act as a homodimer recognizing DR6.

- Nurr-1 target genes are among others:

  * dopamine transporter (reverse transport of dopamine, the most specific protein in dopaminergic neurons)
  * tyrosine hydroxylase (dopamine synthesis)

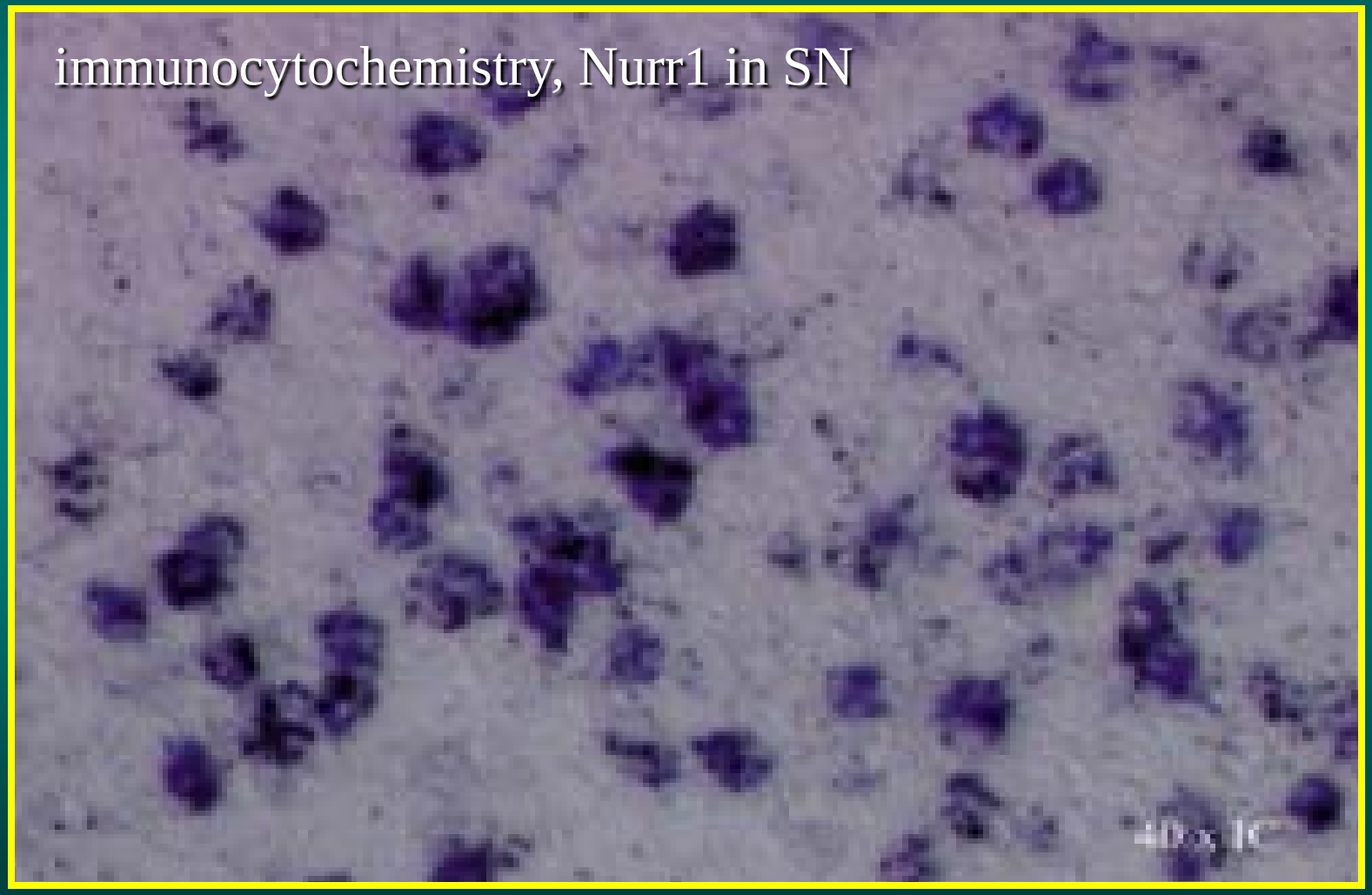
# Co-localization of Nurr1 and TH in the same regions of brain in medaka




*Nurr1 – red staining*

*TH - blue staining*

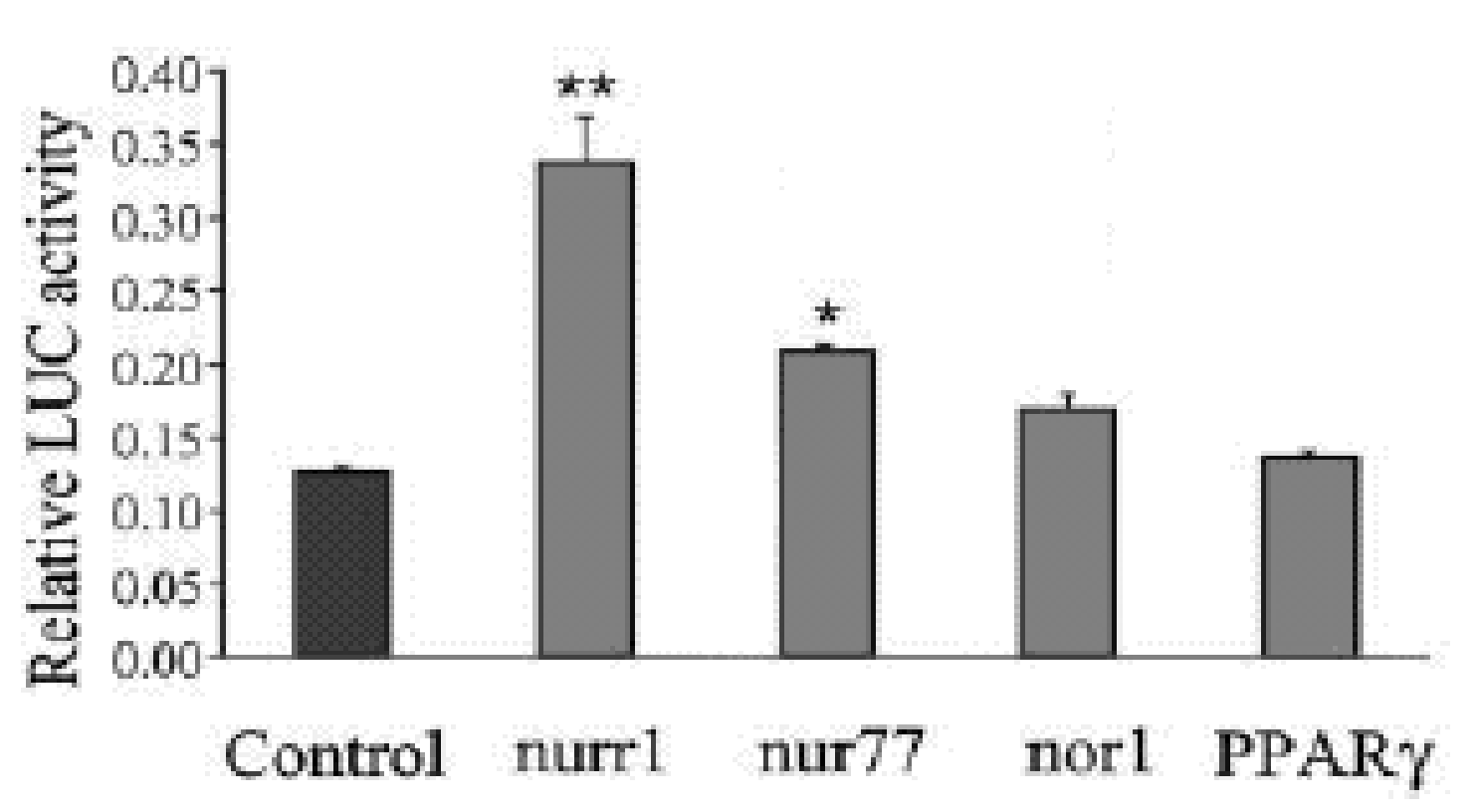
# Nurr1 gene expression in substantia nigra




*Sacchetti et al. J Neurochem 2001*

# Responses of the dopamine transporter gene promoter to members of the nuclear receptor superfamily

*(transfection with different receptor and with reporter construct)*




*Sacchetti et al. J Neurochem 2001*

# Nurr-1 – culture of progenitor cells

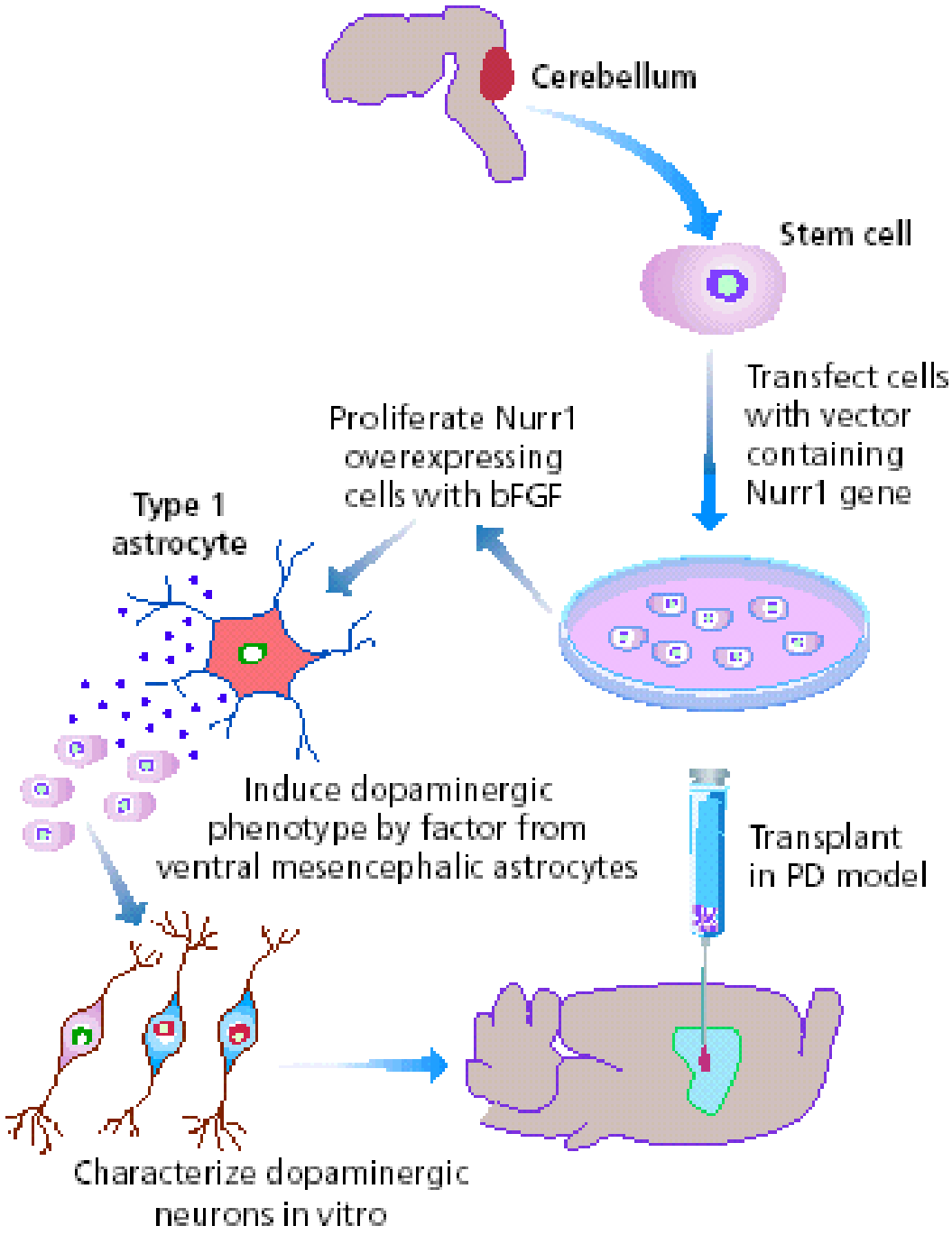
- Nurr-1 is necessary for survival of dopaminergic neurons.

- Nurr-1 overexpression governs the development of progenitor cells toward neurons but these neurons are not dopaminergic (lack of tyrosine hydroxylase) even in the presence of trophic factors and cytokines necessary for dopaminergic neurons.

- When Nurr-1 overexpressing cells are incubated with mesencephalic cells some of them develop into dopaminergic neurons. This process is especially effective in the presence of FGF-2 (bFGF, basic fibroblasts growth factor) and FGF-8.

- The source of signal to differentiation toward dopaminergic neurons are mesencephalic astrocytes. Factor produced by the astrocyte is highly labile, easy diffusible, but is not a ligand for Nurr-1.

- Perhaps Nurr-1 upregulates the expression of receptor recognizing this ligand. Importantly, such pretreated cells transplanted to rats survived well in striatum for at least 2 weeks, although a long term survival is probably weak.




Schematic of the engineering of dopamine neurons for grafting. Stem cells derived from the cerebellum of the mouse are transfected with the Nurr1 gene. When stem cells overexpressing Nurr1 are proliferated with basic fibroblast growth factor (bFGF) and then exposed to a soluble signal secreted by type 1 astrocytes from the ventral mesencephalon, they develop into dopaminergic neurons. These can be implanted in the dopamine-denervated striatum and possibly correct neurochemical and behavioral deficits.

# Thank you (!!) and see you next week (?)

## What would be profitable to remember in June:

- Expression pattern and physiological role of LXR

- Role of PXR, FXR, BXR and SF-1

- Tlx and Nurr1 - role in neuronal development


**Slides and CD can be found in the library and at the Heme Oxygenase Fan Club page:**

**https://biotka.mol.uj.edu.pl/~hemeoxygenase**