

PPARs

Peroxisom proliferator-aktiverte reseptorer

PBF353-2006; Arild Chr. Rustan

PPARs: Classification

Nuclear Receptor Superfamily

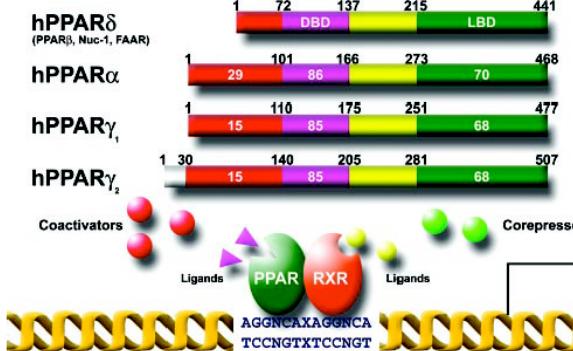
Thyroid Retinoid Steroid PPAR

α β γ

PPARs : Definition

- Nuclear transcription factors
- Activated by various natural and pharmacological ligands
- Change gene expression
- Affect downstream pathways of carbohydrate, lipid and protein metabolism and cell differentiation

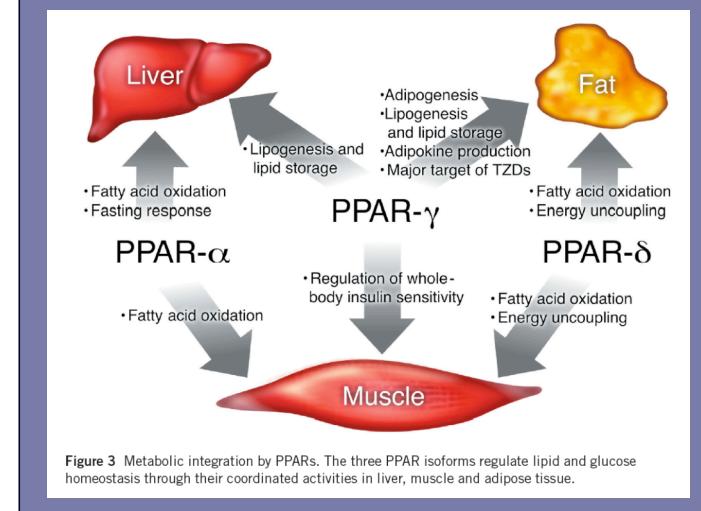
Peroxisome Proliferator-Activated Receptors (PPARs)



Other fatty acid-regulated receptors: RXR (retinoic acid x receptor) and LXR (liver x receptor), and transcription factors, i.e. SREBP-1c and HNF-4

PPARs

- PPAR α
 - Lever, hjerte, skjelettmuskel, tarm
 - Fettsyrereaksydasjon, ketogenese, "glukose-sparing"
- PPAR δ (β)
 - Bred vevsdistribusjon
 - Fettsyrereaksydasjon (skjelettmuskel), energiavkobling
- PPAR γ
 - Fettvev (adipocytter), hvitt og brunt
 - Immunceller (monocytter, makrofager), redusert aterosklerose



PPAR ligander

- Naturlige: Fettsyrer, prostaglandin-analoger (PGJ₂-analog)
- PPAR α agonister: Fibrater (fenofibrat, gemfibrozil), 3-tiafettsyrer, fettsyrer 20:5
 - Lipidsenkende effekt (TAG ↓, HDL ↑)
- PPAR γ agonister: Glitazoner (TZD), umetteide fettsyrer (18:1, 18:2, 20:4, 20:5)

PPARs bind fatty acids

Endogenous ligands			Biological effect
PPAR- α	PPAR- δ	PPAR- γ	
Palmitic acid	Fatty acids	Linoleic acid	Lipid and glucose metabolism
Stearic acid		Arachidonic acid	
Palmitoleic acid		15d-PGJ2	
Oleic acid		9-HODE	
Linoleic acid		13-HODE	
Arachidonic acid		15-HETE	
Eicosapentaenoic acid		Eicosapentaenoic acid	

Pharmacological agonists:

- PPAR- α : fibrates, i.e. gemfibrozil, treat hyperlipidemia
- PPAR- δ : lipophilic carboxylic acids, i.e. GW501516
- PPAR- γ : glitazones, i.e. rosiglitazone, treat insulin resistance

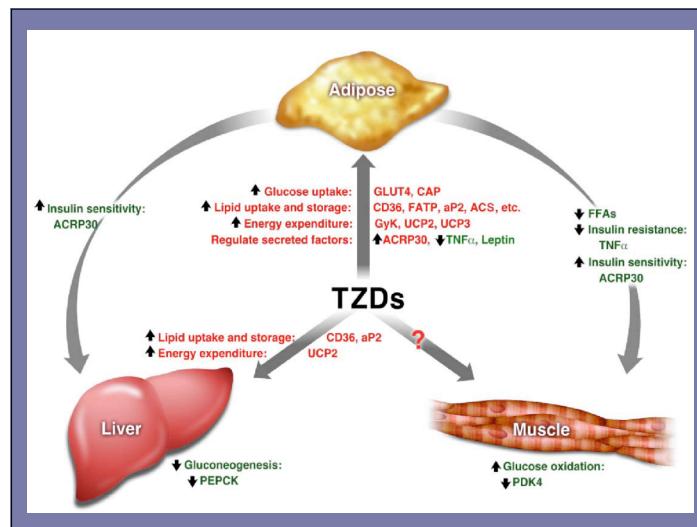
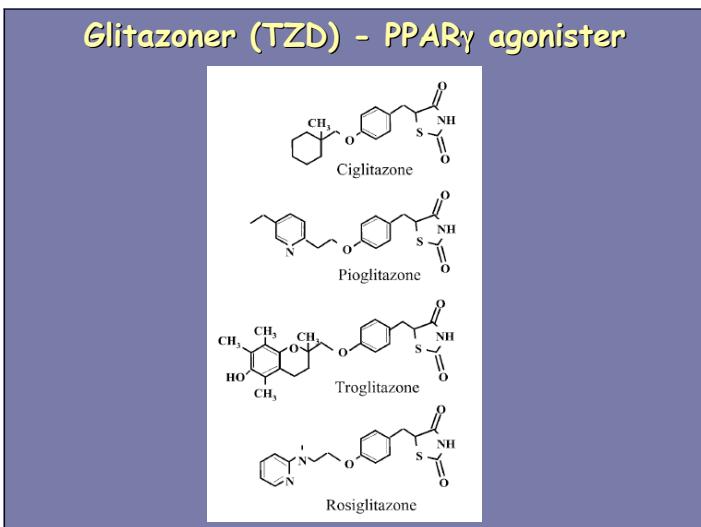
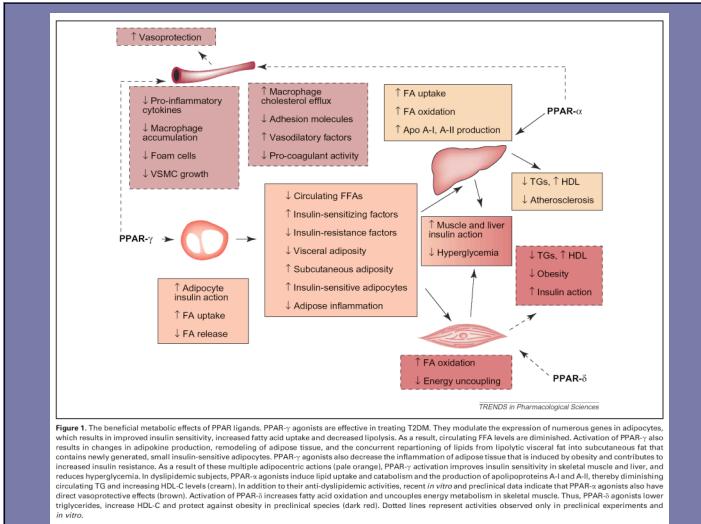


Table 1 —Effect of glitazone therapy on established and emerging CVD risk factors (18)

CVD risk factor	Impact of glitazone therapy
Hyperglycemia	Reduction in A1C
Hypertension	Reduction in blood pressure
Dyslipidemia	Reduction in triglycerides Increase in HDL cholesterol Increase in LDL particle size (less atherogenic particles)
Markers of endothelial inflammation	Decreased C-reactive protein Decreased white blood cell count Decreased fibrinogen Decreased matrix metalloproteinases-9 Decreased tumor necrosis factor- α
Markers of elevated thrombotic risk	Decreased plasminogen activator inhibitor-1 Decreased platelet aggregation