Gene Regulation of Peroxisomal Enzymes by Nutrients, Hormones and Nuclear Signalling Factors in Animal and Human Species

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1. INDUCIBLE AND NON INDUCIBLE PEROXISOMAL ENZYMES

Many peroxisomal enzymes are controlled at the transcriptional level. This gene regulation is well documented in liver from rodent species and is more important upon peroxisome proliferation, although both phenomena are not always associated. Understanding of this regulation comes largely from studies on PPARs (Peroxisome Proliferator-Activated Receptors). Other transcription factors including thyroid hormone receptors, glucocorticoid receptors, LXR, also influence peroxisomal gene expression often in combination with tissue specific cofactors (co-activators or co-repressors). In human tissues and cells, inducibility of peroxisomal enzymes often has not been investigated. De Craemer (1995) reviewed peroxisome proliferation in human liver diseases caused by a large variety of drugs, metabolites, infectious agents or malignancies. Duclos *et al* (1997) and many others found that isolated human liver cells are almost resistant to classical peroxisome proliferators (fibrates). Overexpression of mouse PPARα in human cells does not affect expression of peroxisomal fatty acid β-oxidation enzymes while, in these circumstances, the mitochondrial counterpart is subject to regulation (Hsu *et al.,* 2001; Lawrence et al., 2001). Indeed,

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PPARα activates human muscle carnitine palmitoyl transferase I-CPT I (Mascaro *et al.* 1999). On the other hand, PPAR agonists have been shown to repress human cytochrome CYP4F2-LTB4 ω-hydroxylase promoter (Zhang *et al.* 2000).

Interestingly, a decrease in peroxisome abundance in cultured fibroblasts unrelated to deficiency of a key step in peroxisome biogenesis, is linked to AOX deficiency or defective MFP1 import, suggesting that local metabolism might be involved in organelle formation (Chang *et al.*1999*)*.

In mouse, regulation by fenofibrate of thiolase B gene (see also below) is dependent on PPARα, but differs between tissues. On the contrary, the thiolase-SCPx as well as the other enzymes involved in the branched fatty acid β-oxidation pathway are not inducible by fibrates but they are by a fatty diet (Östlund Farrants *et al.,* 1990) or phytanic acid (Zomer, this Volume). Girnun *et al* (2002) have recently identified a PPRE (PPAR response element) in the rat catalase promoter, although catalase activity is only weakly enhanced by classical peroxisome proliferators.

2. INDUCING FACTORS AND MEDIATORS OF INDUCTION (RECEPTORS)

2.1 Exploratory strategies

A large variety of species have been tested as biological models to reveal either common properties, or specific differences in peroxisome biochemistry and regulation. Rodents (rat, mouse, guinea pig, hamster, etc.) have been largely investigated along with, human, monkey and other animals. Cell lines, primary cultures, yeast or fungi, (see Berteaux-Lecellier, 1995), invertebrates (*C.elegans,* see Petriv *et al.,* 2002), and even plants (*A. thaliana,* see Rylott *et al., 2001*) have also been studied. A noteworthy emerging model for studying peroxisomal gene regulation is the gerbil (*Jaculus orientalis*), a rodent species from the sub desert highland of Morrocco (El Kebbaj *et al.,* 1996) with unique properties of cold adaptation and hibernation. These extreme physiological conditions are associated with adaptative changes in peroxisomal enzymes (Kabine *et al.,* 2003, submitted). Electron microscopy and morphometric analysis in jerboa liver show peroxisome proliferation during cold adaptation (61% increase in numerical density). Palmitoyl-CoA oxidase activity, a peroxisome proliferation marker, increases mainly in brown adipose tissue (4.3 fold) and liver (2 fold) during hibernation, along with an increase in mRNA level in both tissues. Administration of ciprofibrate, a classical peroxisome proliferator, during the pre-hibernation period, leads to hyperinsulinemia and prevents the entry of jerboa into hibernation which is fatal for most animals.

Relationships between peroxisomes and cell differentiation state have been documented in various tissues and organs notably in liver, brain, kidney, muscle, white and brown adipose tissue. Among others, the acyl-CoA oxidase specific activity of human glioblastoma L1 cells increases upon exposure to perfluorododecanoic acid, a peroxisome proliferator, in a cell cycle number dependency (Cimini *et al.,* 2000).

Standard experimental procedures include enzyme/protein immunoblotting, gene organisation, transcriptional and post-transcriptional investigations (nuclear receptors), biochemical signalling, exploration, micro-morphology. Recently, emerging global procedures (genomics, transcriptomics and proteomics screening) and in *vivo* inactivation of targeted genes (null mice and transgenic models) have also been adapted to study peroxisomes. In this respect, a number of mice with KO genes are currently available to research laboratories of most of the β-oxidation enzymes encoding genes, the three PPARs isoforms, several peroxisomal membrane proteins and peroxins (see Berger *et al.*, this volume).

Applications in peroxisomal regulation of RNA interference strategies (see Petriv *et al.,* 2002) and structural biochemistry are just emerging issues. It has been recently shown that interactions of C- and N-terminal domains of peroxisomal MFP1 were required for the hydratase-isomerase activity (Kiema *et al.*, 2002). Moreover, a cDNA microarray screening of PPARα-target gene in mouse liver has revealed that among 7500 genes/EST, there are 246 genes overexpressed (>2fold) in mice given Wy 14, 643 (Cherkaoui Malki *et al* 2001), including PEX11ß, a peroxisomal membrane protein involved in peroxisome biogenesis and ß-oxidation, that was enhanced 6.7-fold.

2.2 Induction by nutrients, hormones and drugs (fig. 2)

Specific ligands are required for nuclear receptor activation. These ligands (or regulatory molecules) are either dietary fatty acids, cholesterol and cholesterol derivatives, biological signalling molecules including thyroid hormones, dehydroepiandrosterone (Sakuma *et al.,* 1993; Depreter *et al.,* 2002), and retinoids, or pharmacological compounds such as fibrates (Reddy *et al.,* 1996), 4-phenylbutyrate (Pineau *et al.,* 1996), statins (Aboushadi *et al.,* 2000) and valproic acid (Lampen *et al.*, 2001).

Thyroid hormone (T3) is a peroxisomal enzyme inducer (Just and Hartl, 1983; Yamada *et al.,* 1994) but decreases the fibrate-dependent induction of peroxisomal acyl-CoA oxidase (Pacot *et al.,* 1993; Chu *et al.,* 1995).

Glucocorticoids are discussed below (2.3).

Fatty acids have peroxisome proliferative activity and increase ß-oxidation enzymes in liver (Thomassen *et al.,* 1982; Van den Branden *et al.,* 1986; Horie and Suga, 1989; Östlund Farrants *et al.,* 1990, and De Craemer *et al.,* 1994). Zipper (1997) reported moderate peroxisome proliferation in rat liver and myocardium upon treatment with ethanol and C22:1 erucic acid and following physical exercise. Nutritional regulation of metabolic genes is further illustrated by the stimulatory effects of fatty acids on LXRα-dependent genes (Tobin *et al.,* 2000) which includes acyl-CoA oxidase and L-bifunctional protein (of which the role in ß-oxidation is unknown: see Wanders *et al.,* this Volume) (Stulnig *et al.,* 2002); by activation of PPARα acyl-CoA oxidase expression with hydroxylated soybean oil (Chao *et al.,* 2001*)* and with conjugated linoleic acid (Moya-Camarena *et al.,* 1999). Other, non-peroxisomal enzymes are upregulated as well. Phytanic and pristanic acids are natural ligands for PPARα and RXR and raise peroxisomal enzymes (Van Den Branden *et al.,* 1986; Zomer *et al.,* 2000). However induction of peroxisomal phytanoyl-CoA hydroxylase by phytanic acid does not involve either PPARα or RXR (Zomer, this Volume). General inducible properties of PPARs have been the topic of many reviews (Vamecq and Latruffe, 1999).

Special attention has been paid to PPARα as a possible physiological sensor in human. Suppression of HNF-4α activity by CoA thioesters of hypolipidaemic peroxisome proliferators may account for hypolipidaemic properties independently of PPAR α activation by their respective unesterified carboxylate forms (Hertz *et al.,* 2001). As a consequence, hypolipidaemic activity of peroxisome proliferators is currently suggested to be mediated by the PPARα or HNF-4 α pathways, in rat and man respectively.

Bile acids (cholic and chenodeoxycholic acids) downregulate mRNA of acyl-CoA oxidase, bifunctional protein and thiolase in mice, and at least for thiolase this effect also occurs in PPARα null mice, so it is PPARα independent (Sinal *et al.,* 2001). In human cells treated with bile acids, peroxisomal enzymes unfortunately were not investigated; hPPARα mRNA was upregulated as well as its target protein the mitochondrial carnitine-palmitoyl transferase I (Pineda Torra *et al.,* 2003).

TNFα decreases PPARα gene and protein expression as well as mRNA of catalase, acyl-CoA oxidase and bifunctional protein in rat liver, while ß-actin is strongly upregulated (Beier *et al.,* 1997).

Vamecq *et al.* (1987) reported on direct inhibitions of rat peroxisomal carnitine-octanoyltransferase and mitochondrial carnitine-palmitoyl-transferase by chlorpromazine (Largactil) a well known anti-depressant. At the same time this compound induces peroxisome proliferation in rodents and it seems also in human liver (Cooper *et al.,* 1989).

2.3 Nuclear signalling factors (fig. 2)

There are multiple interactions reported between PPARα and other nuclear receptors in man and rodents. In agreement with the results of Pacot *et al.,* (1993), the thyroid hormone receptor inhibits activation of PPARs by ciprofibrate, apparently by competition for their common heterodimeric partner RXR (Chu *et al.,* 1995). LXRα antagonizes mouse PPARα/RXRα-mediated transcriptional activation by peroxisome proliferators (Miyata *et al.,* 1996). Bile acids inhibit the effect of PPARα activation at least in part *via* impaired recruitment of transcriptional co-activators (Sinal *et al.,* 2001). The complex CARα/RXRα recognizes the DR2 element of the Hydratase-Dehydrogenase PPRE (Kassam *et al.,* 2000). Fan *et al* (1998) reported increased PPARα level associated with increased fatty acid content in liver from mice with disrupted expression of peroxisomal acyl-CoA oxidase gene.

Upregulation of the PPARα not necessary leads to increased expression of peroxisomal proteins; this is well illustrated by the effect of glucocorticosteroids. Rat hepatocytes in primary culture treated with dexamethasone increase their PPARα protein and mRNA; but acyl-CoA oxidase mRNA is not modified. Dexamethasone however does *potentiate* the well-known induction of oxidase by WY-14643 displaying a circadian rhythm (Lemberger *et al.,* 1996). PPARα is also involved in many cross talks with other nuclear receptors. PPARα and its effects on PPRE through the binding of SMRT (Silencing Mediator for Retinoid and Thyroid hormone receptors) and SHARP (SMRT and Histone deacetylase Associated Repressor Protein) are inhibited by PPAR β (δ) (Shi *et al.,* 2002). A short heterodimer PPAR-RXR lacking DNA binding activates PPARα-RXRα dependent AOX and MFP1 genes (Kassam *et al.,* 2001). STAT5b negatively regulates PPARα (Zhou *et al.,* 2002). RIP140 negatively interacts with PPARα and LXRα (Miyata *et al.,* 1998). P300 activates PPARα and PPAR β (δ) in CaCo2 cells (Mochizuki *et al.,* 2002); PRIC285 functions as a co-activator for PPARα (Surapureddi *et al.,* 2002).

Cross-talks of PPAR isoforms with the general cell signalling transduction pathways have been further documented. Protein kinase A activates PPARα through a higher stability of the PPAR phosphorylated form-DNA complex in mouse (Lazennec *et al.,* 2000). The *P38*-MAP kinase activates PPARγ through an increase of PGC-1 coactivator binding to PPARγ in mouse myocytes (Barger *et al.,* 2002).

Interestingly, some target gene products self activate PPAR. HMG-CoA synthase, a mitochondrial ketogenic enzyme, regulates its gene expression by association with PPARα (Meertens *et al.,* 1998); so does *in-vitro* translated peroxisomal bifunctional enzyme by interaction with the N-

terminus of PPARα, which represents a peroxisomal-nuclear regulatory loop (Juge-Aubry *et al.*, 2001).

3. STUDY OF KEY ENZYMES AT THE GENE LEVEL

Recent research in our lab has focused on four peroxisomal proteins in rodents (figure 1); the membrane ABC transporters (Bugaut *et al.*, 2003, this issue), the farnesyl pyrophosphate synthase (Le Jossic-Corcos *et al.*, 2003, this issue) in relationship with PPAR (Motojima *et al.*, 1998), the bifunctional enzyme (Caira *et al.*, 1998) and the inducible thiolase B (Table I, fig. 1). Peroxisomal 3-ketoacyl-CoA thiolase encoded in humans by only one gene is in rodents (rat and mouse) produced by two (thiolase A and B) genes whose encoding sequence in mouse display ≈97 % nucleotide sequence identity (Chevillard *et al.*, this Volume). Thiolase A gene is constitutive and expressed mainly in liver and intestine while thiolase B gene is strongly induced by peroxisome proliferators in liver while to a little extent in kidney, intestine and white adipose tissue. The promoter-located PPRE of the latter enzyme, not only interacts with PPARα but also with HNF-4 which activated luciferase gene expression driven by the putative thiolase PPRE (Nicolas-Francès *et al.*, 2000). As a suggestion, thiolase B gene induction by peroxisome proliferators might be mediated *via* either recruitment of other regulatory elements or *via* additional PPRE sequences, all of which remain to be determined to explain this potent induction by peroxisome proliferators.

Table I - Different rat thiolases

Peroxisome	Mitochondria	Cytosol
*3-ketoacyl-CoA thiolase or thiolase A (constitutive at a low level) role in third step of β-oxidation of very long straight-chain fatty acids	3-ketoacyl-CoA thiolase (β-oxidation of medium and long chain fatty acids)	acetoacetyl-CoA thiolase (role in cholesterol synthesis)
*3-ketoacyl-CoA thiolase or thiolase B (same substrate specificity of thiolase A inducible by various hypolipidaemic compounds)	acetoacetyl-CoA thiolase (major role in ketone body metabolism)	
*3-ketoacyl-CoA thiolase-sterol carrier protein-X = SCP-X (role in β-oxidation of branched carbon substrates)	β-subunit of trifunctional enzyme (third step of long chain fatty acids β-oxidation cycle)	
*acetoacetyl-CoA thiolase (role in cholesterol and ketone body synthesis)		

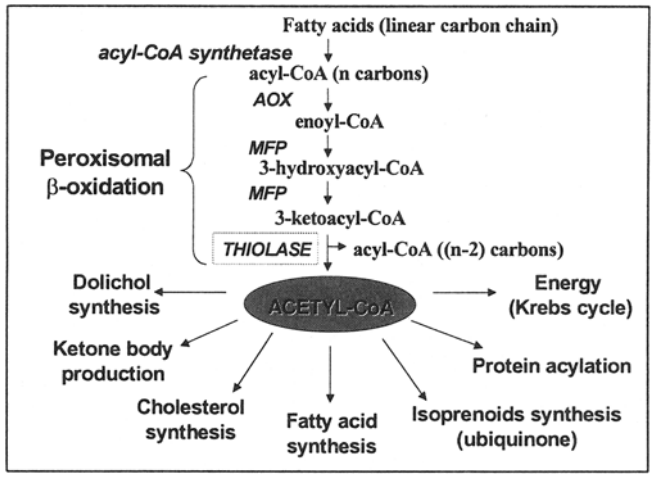

Figure 1. Metabolic position of peroxisomal thiolase.

3. CONCLUSION

The great amount of data published on PPAR clearly indicates that in animals, PPARα receptor is a key element in the peroxisomal enzymes regulation by fatty acids, hormones and xenobiotics. Figure 2 (top) illustrates that in rodents, PPARα is controlled either positively or negatively in multiple ways. Cholesterol regulates the FPP synthase, a key step on the peroxisomal cholesterol synthesis pathway, through SREBP as transcription factor. Attempts to explain large variations in peroxisomal enzyme gene expression should consider differences in the diet between species (fig. 2 top), which in rodent is mainly based on carbohydrates except for the suckling period, and in human consists of a mixed diet containing carbohydrates, fat and protids. In the latter dietary conditions, peroxisomal enzymes appear largely constitutively expressed or at least unsensitive to PPARα. This is not the case for mitochondrial fatty acid β-oxidation protein (fig. 2-bottom) which apparently keeps inducible properties like in rodents. It should be pointed out that human peroxisomal hydratase dehydrogenase (MFP2) encoding gene is modulated in a PPAR independent manner. Here the AP2 transcription factor 2 activates while Sp1 represses activity (Novikov and Kamps, 2001).

Attempts to correct human peroxisomal diseases are in progress using nutritional and pharmacological therapy through the ABC encoding genes redundancy approach (Bugaut *et al.*, 2003, this Volume).

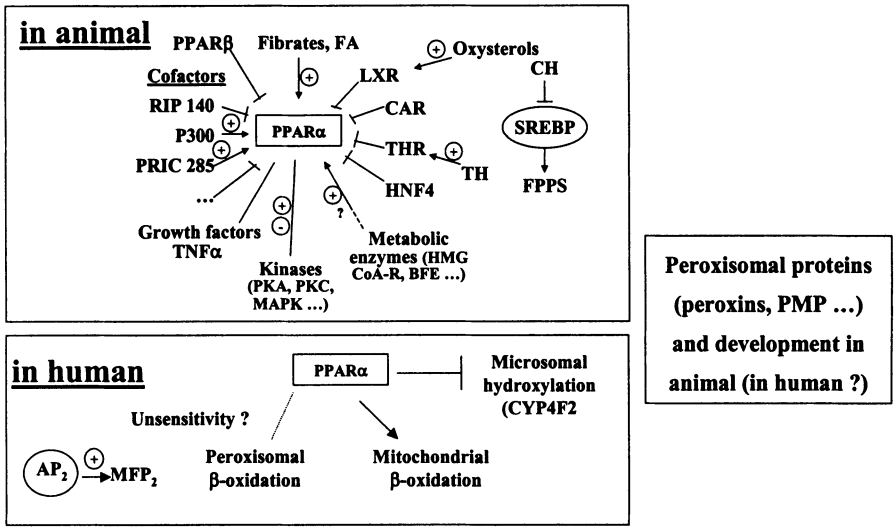

Figure 2. Summary of regulation of peroxisomal enzymes by nutrients, hormones and nuclear signalling factors in animal (top) and in human (bottom) species.

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