Peroxisome proliferator-activated receptors: a nuclear hormone receptor involved in adipocyte differentiation and lipid homeostasis

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The peroxisome proliferator-activated receptors (PPARs) were, until recently, orphan receptors with no known ligand and an unclear physiological role. Since the recent discovery of PPAR ligands and their effect on adipocyte differentiation, this receptor is now speculated to be possibly implicated in the pathogenesis of insulin resistance and obesity. The PPARs belong to the superfamily of nuclear hormone receptors (together with steroid, thyroid hormone, retinoid and vitamin D receptors) which act as transcription factors. PPARs recognize and bind to specific DNA sequences (response elements) in the promoter region of target genes as a heterodimer with the 9-cis-retinoic acid receptor RXR. While PPAR can bind to DNA in the unliganded state, ligand binding is essential for activation of the PPAR and the resulting induction of target gene expression. The known target genes are mostly coding for lipolytic enzymes involved in peroxisomal fatty acid β-oxidation.

So far, three PPAR subtypes PPAR-α, PPAR-β (and its homologs δ/NUC-1) and PPAR-γ have been described. The tissue distribution of these receptors was studied at the mRNA level by the group of Walter Wahli in the adult rat, revealing a ubiquitous expression of PPAR-β, whereas PPAR-α was found to be expressed predominantly in liver and PPAR-γ mRNA content was highest in the spleen and adipose tissue. These findings support the authors’ suggestion that PPAR-α might mediate fatty acid oxidation, whereas PPAR-γ would stimulate lipid accumulation. Besides its metabolic functions, PPAR-γ has been shown more recently by Bruce Spiegelman’s group to be crucial for early adipocyte differentiation. The expression and ligand-dependent activation of PPAR-γ was sufficient to induce adipocyte differentiation in 3T3-L1 fibroblasts. The same group was able to demonstrate that ectopic expression of PPAR-γ in myoblasts is acting as a developmental switch by inhibiting myogenesis and participating in the induction of adipogenesis, which confirms the key role of PPAR-γ in determining the adipocyte phenotype.

The first agents described to activate PPARs were so-called peroxisome proliferators, including hypolipidemic drugs (e.g., clofibrate), plasticizers, herbicides and organic solvents, which are known to induce peroxisome proliferation and hepatocarcinoma in rodents. However, for as yet unknown reasons, fibrates seem to cause neither peroxisome proliferation nor hepatocarcinoma in humans. Walter Wahli’s group was previously able to show that long-chain fatty acids are weak PPAR activators, while a synthetic arachidonic acid analog (5,8,11,14-eicosatetraynoic acid, ETYA) was a potent activator of PPAR (4). Despite the fact that peroxisome proliferators and fatty acids are activating PPAR, no direct binding of these substances to PPAR could be demonstrated. Lacking a true ligand, PPAR remained an orphan receptor until Lehmann and co-workers identified the antidiabetic thiazolidinediones as high-affinity ligands for PPAR-γ (Kd 40 nmol/l) (5). They therefore suggested that PPAR-γ might be the target for the antidiabetic effects of the insulin-sensitizing thiazolidinediones, possibly by reducing peripheral insulin resistance through a PPAR-dependent decrease in the adipose synthesis of tumor necrosis factor α and its receptor, the latter cytokine being well known to impair insulin action.

Recently, two independent groups reported in the same issue of Cell the first natural ligand of PPAR-γ: 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2), a prostaglandin J2 (PGJ2) metabolite (7, 8). As the arachidonic acid analog ETYA was already known to activate PPAR, the hypothesis was put forward that arachidonic acid metabolites might bind to PPAR. Arachidonic acid released from membrane phospholipids is converted by cyclooxygenase before being metabolized further to yield the various groups of PGs, including PGJ2. While most PGs are known to act through G-protein-coupled membrane-bound receptors, PGJ2 metabolites were found previously to accumulate in the nucleus and hence were speculated to regulate directly gene expression. A potential carrier protein is the liver fatty acid binding protein to which PGJ2 binds, which is a protein whose expression is regulated by PPAR itself. The PGJ2 metabolites are cyclopentenones, which differ in many respects from other PGs (9). The PGJ2 effects include suppression of viral replication, cell cycle inhibition, induction of heat-shock protein expression and stimulation of osteogenesis. Both groups were screening different PGs for their ability to activate and bind PPAR and found that PGD2 and its dehydration product PGJ2 were able to activate PPAR-γ in transient transfection assays, but that only 15d-PGJ2, the end-product of PGD2 metabolism, was a relatively high-affinity ligand for PPAR-γ in that it was effectively displacing the thiazolidinedione compound (Kd in the μmol/l range). Effects of PGJ2 on PPAR-α were several-
fold weaker, suggesting a subtype specificity. However, the local tissue concentrations of the various PGJ2 metabolites are not known and hence their relative impact on the activation of PPAR-α and PPAR-γ in vivo cannot be inferred readily. Furthermore, 15d-PGJ2 was able to stimulate PPAR-γ-mediated conversion of fibroblasts into adipocytes and to induce lipogenesis, confirming its biological potency. 12-Deoxy-PGJ2, a precursor of 15d-PGJ2, is found in human urine and results from spontaneous conversion of PGD2 in the presence of albumin. Hence, J2 prostaglandins seem to be present normally in the human body.

Thus, PPAR-γ has finally a natural ligand and PGJ2 metabolites have found a nuclear target protein, suggesting that adipogenic prostanoids are playing an important role in lipid homeostasis, adipocyte differentiation and possibly insulin resistance. The anti-diabetic thiazolidinedione being a PPAR-γ ligand reinforces the potential pathogenetic and/or therapeutic importance of this receptor in non-insulin-dependent diabetes mellitus, although no direct evidence is currently available. Further data on the physiological importance of this nuclear receptor will be obtained by PPAR-γ knock-out models, although the various subtypes might result in considerable redundancy, as illustrated by the PPAR-α-deficient transgenic mouse showing no phenotype (10).

References

Calcium-sensing receptor: confirmation of its pivotal function in calcium homeostasis, using a knock-out model

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Very small changes in ionized calcium induce rapid changes in PTH secretion in order to keep the extracellular calcium concentration constant or within its narrow normal range. For nearly 20 years, clinical investigations and in vitro studies have suggested that sensing extracellular calcium is altered in various disorders of plasma calcium regulation. Set point abnormalities in the regulation of PTH secretion by extracellular calcium have been established in various diseases, such as hyperparathyroidism and familial benign hypocalciuric hypercalcaemia (FBBH). The calcium sensing receptor (CaSR) was recently cloned from bovine parathyroid tissue. This receptor enables the parathyroid cells to detect and respond to these minute changes. It is a 120-kD polypeptide with seven transmembrane domains characteristic of the superfamily of G protein-coupled cell surface receptors and with a very large extracellular N-terminal domain that resembles metabotropic glutamate receptors. Functional studies using chimeras of metabotropic glutamate and calcium receptor suggest that the extracellular domain of the CaSR is the major binding site for extracellular calcium. An activated CaSR produces an increase in cytosolic free calcium concentration via activation of the phospholipase C/inositol triphosphate signal transduction pathway. The CaSR gene is located on chromosome 3q.

Familial benign hypocalciuric hypercalcaemia is an autosomal dominant benign disorder associating hypercalcaemia, low urinary calcium excretion and very few