Peroxisome proliferator-activated receptor

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Abstract: The peroxisome proliferator-activated receptors (PPARs) belong to the nuclear hormone receptor superfamily. All PPARs heterodimerize with the retinoid X receptor (RXR) and bind to specific regions on the DNA of target genes. The discovery of PPARγ as a target of multimodal insulin sensitizers has attracted remarkable scientific interest and had a great impact on the pharmaceutical industry. This article gives a review for the PPAR. [Nature and Science. 2008;6(4):64-70]. ISSN: 1545-0740.

Keywords: peroxisome proliferator-activated receptor (PPAR); protein; phiology

Introduction

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily of ligand-activated transcription factors that are related to retinoid, steroid, and thyroid hormone receptors (Esposito et al. 2006). Three types of PPARs have been identified: α (alpha), γ (gamma), and β/δ (beta/delta): α (expressed in liver, kidney, heart, muscle, adipose tissue); β/δ (expressed in many tissues but markedly in brain, adipose tissue) γ (through alternative splicing is expressed in three forms: γ1 - expressed in virtually all tissues, including heart, muscle, colon, kidney, pancreas, and spleen γ2 - expressed mainly in adipose tissue, γ3 - expressed in macrophages, large intestine, white adipose tissue) (Sridhar 2003).

Discovery of peroxisome proliferator-activated receptor

PPARs were originally identified in Xenopus frogs as receptors that induce the proliferation of peroxisomes in cells. The first PPAR (PPARα) was discovered during the search of a molecular target for a group of agents then referred to as peroxisome proliferators, as they increased peroxisomal numbers in rodent liver tissue, apart from improving insulin sensitivity. After PPARδ was identified in humans in 1992, it turned out to be closely-related to the PPARβ previously described during the same year in other animals. The name PPARδ is generally used in the US, whereas the use of the PPARβ denomination has remained in Europe where this receptor was initially discovered in Xenopus. These agents, pharmacologically related to the fibrates were discovered in the early 1980s. When it turned out that PPARs played a much more versatile role in biology, the agents were in turn termed PPAR ligands. The best-known PPAR ligands are the thiazolidinediones (Krey et al. 1997). (http://en.wikipedia.org/wiki/Peroxisome_proliferator-activated_receptor).

PPAR γ is the subject of intense investigation as a target for drugs against diabetes, atherosclerosis and cancer. For this reason there is considerable interest in the spectrum of compounds that bind this receptor. The binding of this fatty acid to the receptor increases its fluorescence and causes a shift in the UV spectrum. This spectral shift is reversible by competition with other known ligands for PPARγ. This report represents the first direct demonstration of a fatty acid binding to PPARγ (Palmer and Wolf 1998). In Kasuga's study, 3-(4-Alkoxyphenyl)propanoic acid derivatives were prepared as candidate PPAR α/δ/γ pan agonists, based on our previous SAR studies directed toward the development of subtype-selective PPAR agonists. The steric bulkiness of substituents introduced at the distal benzene ring had an important influence on PPAR activity. The finding that a 4-adamantyl derivative exhibited not only PPARα/δ activity but also significant PPARγ activity prompted us to search for structurally novel phenylpropanoic acid derivatives with more potent adipocyte differentiation activity than the well-known PPARγ agonist, rosiglitazone, as well as well-balanced PPARα and PPARδ agonistic activities (Kasuga et al. 2008). The PPAR γ is one of the ligand-activated transcription factors in the nuclear hormone receptor superfamily and

a pivotal regulator of glucose and lipid homeostasis. The discovery of PPARγ as a target of multimodal insulin sensitizers, represented by thiazolidinediones (TZDs), has attracted remarkable scientific interest and had a great impact on the pharmaceutical industry. With the clinical success of the PPARγ agonists, pioglitazone (Actos) and rosiglitazone (Avandia), development of novel and potent insulin-sensitizing agents with diverse clinical profiles has been accelerated (Cho and Momose 2008). The physiological role of PPARδ may be an indicator for switching from glucose metabolism to fatty acid metabolism (Takahashi et al. 2006).

Structure of Peroxisome proliferator-activated receptor

Like other nuclear receptors, PPARs are modular in structure and contain the following functional domains: (A/B) N-terminal region; (C) DBD (DNA-binding domain); (D) flexible hinge region; (E) LBD (ligand binding domain); (F) C-terminal region. The DBD contains two zinc finger motifs, which bind to specific sequences of DNA known as hormone response elements when the receptor is activated. The LBD has an extensive secondary structure consisting of 13 α helices and a β sheet. Natural and synthetic ligands bind to the LBD, either activating or repressing the receptor (Yee et al. 1997) (http://en.wikipedia.org/wiki/Peroxisome_proliferator-activated_receptor).

The PPARs belong to the nuclear hormone receptor superfamily. To date, three different PPAR isotypes, namely PPARα, -δ, and -γ, have been identified in vertebrates and have distinct patterns of tissue distribution. Like all nuclear receptors, the human PPARγ (hPPARγ) is characterized by a modular structure composed of an N-terminal A/B domain, a DNA-binding domain with two zinc fingers (C domain), a D domain, and a C-terminal ligand-binding domain (E/F domain). Human PPARγ exists in two protein isoforms, hPPARγ(1) and -γ(2), with different lengths of the N-terminal. The hPPARγ(2) isoform is predominantly expressed in adipose tissue, whereas hPPAR-γ(1) is relatively widely expressed. Human PPARγ plays a critical physiological role as a central transcriptional regulator of both adipogenic and lipogenic programs. Its transcriptional activity is induced by the binding of endogenous and synthetic lipophilic ligands, which has led to the determination of many roles for PPAR-γ in pathological states such as type 2 diabetes, atherosclerosis, inflammation, and cancer. Of the synthetic ligands, the thiazolidinedione class of insulin-sensitizing drugs (ciglitazone, pioglitazone, troglitazone, rosiglitazone) is employed clinically in patients with type 2 diabetes (Zieleniak et al. 2008). The structure of the complex with the S-enantiomer reveals a new region of the PPARγ-LBD never sampled before by other ligands (Montanari et al. 2008).

Amri et al detected the primary sequence of human PPAR in 1995. According to Amri's study, exposure of preadipocytes to long chain fatty acids induces expression of several gene markers of adipocyte differentiation. The cDNA had the characteristics and ligand-binding domains of nuclear hormone receptors and encoded a 440 amino acid protein related to PPARs, PPAR. The deduced protein sequence was 88% homologous to that of hNUC I, isolated from human osteosarcoma cells. The human PPAR primary sequence is following (Amri et al. 1995):

1 meqpqeetpe areeekeeva mgdgapelng gpehtlpsss cadlsqnssp sslldqlqmg
61 cdgasggsln mecrvcgdka sgfhygvhac egckgffrrt irmkleyekc drickiqkkn
121 rnkcqycrfq kclalgmshn airfgrmpea ekrklvaglt asegcqhnpq ladlkafskh
181 iynaylknfn mtkkkarsil tgkss hnapf vihdietlwq aekglvwkql vnglppynei
241 svhvfyrcqs ttvetvrelt efaknipnfs slflndqvtl lkygvheaif amlasivnkd
301 gllvangsgf vtheflrslr kpfsdiiepk fefavkfnal elddsdlalf iaaiilcgdr
361 pglmnvpqve aiqdtilral efhlqvnhpd sqylfpkllq kmadlrqlvt ehaqmmqwlk
421 ktesetllhp llqeiykdmy

Studied by Sher et al in 1993, the human PPAR was cloned from a human liver cDNA library. The cDNA exhibited 85% and 91% DNA and deduced amino acid sequence identity with mouse PPAR (mPPAR), respectively. The hPPAR gene was mapped on human chromosome 22 slightly telomeric to a linkage group of six genes and genetic markers that are located in the general region 22q12-q13.1. Cotransfection assays of mouse Hepa 1 cells were used to roughly compare the ability of hPPAR- and mPPAR-expressed cDNAs to trans-activate the acyl CoA oxidase (ACO) PPAR response element located 5' upstream to the minimal thymidine kinase promoter driving the expression of the chloramphenicol acetyl transferase (CAT) reporter gene. Both receptors elicited a response with the prototypical peroxisome proliferators nafenopin, clofibrate, and WY-14,643. Moreover, using cotransfection assays in which the

CAT reporter plasmid contained the CYP4 A6 gene response element rather than the ACO element, it was shown that hPPAR is capable of very efficiently trans-activating a second PPAR response element. These results indicate that the PPAR is present in humans in a form that is functional and can trans-activate response elements derived from two different genes, the rat ACO and the rabbit CYP4A6. The primary sequence of 468 amino acids of human PPAR detected by Sher et al in 1993 is as the following (Sher et al. 1993):

1 mvdtesplcp lspleagdle splseeflqe mgniqeisqs igedssgsfg fteyqylgsc
61 pgsdgsvitd tlspasspss vtypvvpgsv despsgalni ecricgdkas gyhygvhace
121 gckgffrrti rlklvydkcd rsckiqkknr nkcqycrfhk clsvgmshna irfgrmprse
181 kaklkaeilt cehdiedset adlkslakri yeaylknfnm nkvkarvils gkasnnppfv
241 ihdmetlcma ektlvaklva ngiqnkevev rifhccqcts vetvteltef akaipafanl
301 dlndqvtllk ygvyeaifam lssvmnkdgm lvaygngfit reflkslrkp fcdimepkfd
361 famkfnalel ddsdislfva aiiccgdrpg llnvghiekm qegivhvlrl hlqsnhpddi
421 flfpkllqkm adlrqlvteh aqlvqiikkt esdaalhpll qeiyrdmy

The human PPAR gene encodes a component of SCF complexes, which are composed of this protein, cullin 1, a ring-box protein, and one member of the F-box family of proteins. This protein binds directly to the F-box motif found in F-box proteins. SCF complexes are involved in the regulated ubiquitination of specific protein substrates, which targets them for degradation by the proteosome. Specific F-box proteins recognize different target protein(s), and many specific SCF substrates have been identified including regulators of cell cycle progression and development. Studies have also characterized the protein as an RNA polymerase II elongation factor. Alternative splicing of this gene results in two transcript variants. A related pseudogene has been identified on chromosome 7. Transcript Variant: This variant (2) utilizes an alternate splice site in the 3' coding region, compared to variant 1. This results in a frameshift and slightly longer protein (isoform b), compared to isoform a. The human PPAR gene sequence is as the following (Chen et al. 1995):

1 agccgcgatg tgacgccgcg cgccccgggg tcctcggcgc ctgcgccctc tcctataaag
61 cagacgccgc gccgcgctgc gacgctgtag tggcttcgtc ttcggttttt ctcttccttc
121 gctaacgcct cccggctctc gtcagcctcc cgccggccgt ctccttaaca ccgaacacca
181 tgccttcaat taagttgcag agttctgatg gagagatatt tgaagttgat gtggaaattg
241 ccaaacaatc tgtgactatt aagaccatgt tggaagattt gggaatggat gatgaaggag
301 atgatgaccc agttcctcta ccaaatgtga atgcagcaat attaaaaaag gtcattcagt
361 ggtgcaccca ccacaaggat gaccctcctc ctcctgaaga tgatgagaac aaagaaaagc
421 gaacagatga tatccctgtt tgggaccaag aattcctgaa agttgaccaa ggaacacttt
481 ttgaactcat tctggctgca aactacttag acatcaaagg tttgcttgat gttacatgca
541 agactgttgc caatatgatc aaggggaaaa ctcctgagga gattcgcaag accttcaata
601 tcaaaaatga ctttactgaa gaggaggaag cccaggtacg caaagagaac cagtggtgtg
661 aagagaagtg aaatgttgtg cctgacactg taacactgta aggattgttc caaatactag
721 ttgcactgct ctgtttataa ttgttaatat tagacaaaca gtagacaaat gcagcagcaa
781 gtcaattgta ttagcagaat attgtcctca ttgcatgtgt agtttgagca cagatcccaa
841 accttacggc caagtttctt ctagtatgat ggaaagtttc ttttttcttt gctctgaata
901 aaactgaact gtgggttctc tataagtggc attttgggct ttccctcttt tttgtaaagc
961 aatgtctgcc tagtttattg tccagttaac tttagtgacc ttttaaaagt tggcattgta
1021 aataaaacaa cttgcaaaaa agttttctgg aatagaatta acaaaatatt atctttattc
1081 atgagttgga aactggaaaa aggcttcttg aagtaaatgt tctgagtgga gctactagga
1141 tgtcttccag cctcctgcag tcaaggagta ccactgtatt gattagcctg tatgtagcag
1201 ggctcccttc attgcatctg aggacttgtt ttctttttct ttatttttaa tcctcttagt
1261 tttaaatata ttgcctagag actcagttac tacccagttt gtggtttttt gggagaaatg
1321 taactggaca gttagctttt caattaaaaa gacacttaac ccatgtggga tgtcatcttt
1381 ttataattag tgttcccatg tggagaaaat tattcacact acttgcatgt aaagaataat
1441 ttaactttta acattaaaat atgtggtaaa acccagaaag catccatcat gaatgcaaga
1501 tactttcaat aaaaagtaag ttatatagta ggtagttaag tttgcttttg tggacttaaa
1561 tgtgtctctt cacttaaatg ggttgaatgt gtatatattt gttcagcttg aaaagactta
1621 gtttatatcc tagctcactg gaggctgctg acataaccat aacttctgtc ccttctaatt

1681 gtcatttata tgcctaactg gagctagtac tttaattctt aacacaaaat tactctgcca
1741 ttgtttccag cttccctcct acaatagaat gaagtttttt tgatggcttg agatggctca
1801 caaattttga ttttttttc ttccttgtgc tcccttttt tctccttgct tttccagtta
1861 acatctatat tcacatgtaa tcttgttttc tcttcacatt cactgagttg ttcaggctca
1921 gatcatccct tgacagtagt ttgccttcat ctcacctttc atttgtccca aattcacctt
1981 atttaataaa gtcccatatg ttgtctcact taaaaaaaaa aaaaaaaa

Physiological function of Peroxisome proliferator-activated receptor

All PPARs heterodimerize with the retinoid X receptor (RXR) and bind to specific regions on the DNA of target genes. These DNA sequences are termed PPREs (peroxisome proliferator hormone response elements). The DNA consensus sequence is AGGTCAXAGGTCA, with X being a random nucleotide. In general, this sequence occurs in the promotor region of a gene, and, when the PPAR binds its ligand, transcription of target genes is increased or decreased, depending on the gene. The RXR also forms a heterodimer with a number of other receptors (e.g., vitamin D and thyroid hormone) (Raingeard et al. 2009).

The function of PPARs is modified by the precise shape of their ligand-binding domain (see below) induced by ligand binding and by a number of coactivator and corepressor proteins, the presence of which can stimulate or inhibit receptor function, respectively (Zieleniak et al. 2008).

Endogenous ligands for the PPARs include free fatty acids and eicosanoids. PPARγ is activated by PGJ_2 (a prostaglandin). In contrast, PPARα is activated by leukotriene B_4 (Yu and Reddy 2007; Zieleniak et al. 2008) (http://en.wikipedia.org/wiki/Peroxisome_proliferator-activated_receptor).

Human PPARγ plays a critical physiological role as a central transcriptional regulator of both adipogenic and lipogenic programs. Its transcriptional activity is induced by the binding of endogenous and synthetic lipophilic ligands, which has led to the determination of many roles for PPARγ in pathological states such as type 2 diabetes, atherosclerosis, inflammation, and cancer (Zieleniak et al. 2008).

PPARγ is a nuclear receptor that is known to have a tumour suppressor role in cancer. PPARγ also acts as a receptor for polyunsaturated fatty acids, including omega-3 and 6 (Yasui et al. 2005; Yasui et al. 2006).

Medical applications of Peroxisome proliferator-activated receptor

The reproductive function of PPARδ was first revealed in the uterus at the implantation site. Since then, PPARδ and its ligand have been discovered in all reproductive tissues, including the gametes and the preimplantation embryos. PPARδ in preimplantation embryos is normally activated by oviduct-derived PPARδ ligand. PPARδ activation is associated with an increase in embryonic cell proliferation and a decrease in programmed cell death (apoptosis). On the other hand, the role of PPARδ and its ligand in gamete formation and function is less well understood (Huang 2008). Lee et al have applied the fluorescent differential method and the PPARα-null mouse model for the rapid isolation of expression tags of PPARα target genes that are involved in the action of peroxisome proliferators and in the regulation of lipid homeostasis under energy deprivation. Identification of a wide spectrum of PPARα target genes will provide new insights into the diverse cellular pathways regulated by these receptor, and this information will be critical for understanding the complicated biological interactions among members of the PPARα target genes. With the recent technological advancement, a newer method, such as DNA microarray, has emerged in the identification of differential gene expressions. This new DNA microarray method, in conjunction with the differential display method, is the first important step toward understanding the molecular mechanisms of gene interactions in any biological systems and can speed up the search for differential gene expressions (Lee et al. 2002).

Discussion

The prevalence of type 2 diabetes continues to expand worldwide. Increased body mass index (BMI), preexisting glucose and insulin abnormalities, physical inactivity, and parental diabetes appear to be acknowledged risk factors for the development of new diabetes. In 1997, the American Diabetes Association (ADA) adopted new criteria for the detection of diabetes by establishing a single fasting blood glucose of at least 126 mg/dL (7 mmol/L) for the diagnosis of overt diabetes and glucose levels of 110 to 125 mg/dL (6.1 to 6.9 mmol/L) for impaired fasting glucose. People who develop type 2 diabetes usually pass through the phases of excessive adipogenesis, nuclear peroxisome proliferator–activated receptor (PPAR) modulation, insulin resistance, hyperinsulinemia, pancreatic ß-cell stress and damage leading to a

progressive decrease in insulin secretion, and impaired glucose postprandial and fasting levels. Fasting glucose is presumed to remain normal as long as insulin hypersecretion can compensate for insulin resistance. The profound metabolic (specifically glucose and fatty acids) abnormalities associated with the impaired fasting glucose phase lead to further disturbance of insulin sensitization and secretion. These mechanisms contribute to the conversion of the impaired fasting glucose phase to overt diabetes. PPAR-α is activated by fibric acids (eg, bezafibrate) and form heterodimers with the 9-cis retinoic acid receptor. These heterodimers bind to peroxisome proliferator response elements, which are located in numerous gene promoters and increase the level of the expression of mRNAs encoded by PPAR-α target genes (Tenenbaum et al. 2004).

Activation of PPARα by clofibrate has recently been shown to cause upregulation of the high-affinity carnitine transporter novel organic cation transporter (OCTN) 2 in small intestine. This strongly suggests that PPARα activation in response to clofibrate treatment improves the absorption of carnitine from the diet. The administration of clofibrate to rats increases carnitine absorption in small intestine which is probably due to the observed upregulation of OCTN2 mediated by activation of PPARα (Ringseis et al. 2008). PPARγ activation by rosiglitazone attenuates mitochondrial dysfunction in mutant huntingtin-expressing striatal cells, and this could be an important therapeutic avenue to ameliorate the mitochondrial dysfunction that occurs in Huntington disease (Quintanilla et al. 2008). PPAR-γ ligands constitute important insulin sensitizers that have already been used for the treatment of human metabolic disorders, exerting also pleiotropic effects on inflammatory related diseases and cancer. Ischemia-reperfusion injury that is mainly associated with organ transplantation constitutes a serious complication with a great relevance in clinical practice. PPAR-γ ligands seem to represent potential therapeutic agents in the aim to reduce or even prevent injury associated with ischemia-reperfusion (Giaginis et al. 2008). PPARγ is expressed in a variety of immune cells as well as in numerous leukemias and lymphomas. Understanding the diverse properties of PPARγ ligands is crucial for the development of new therapeutic approaches for hematological malignancies (Garcia-Bates et al. 2008). Rosiglitazone, a drug that has an excellent safety profile, may offer a well tolerated systemic treatment option for atopic dermatitis. However, its role should be further assessed in controlled trials to establish its efficacy and safety in this disease (Behshad et al. 2008).

Melanomacrophages, cells of the immune system in fish, show strong expression of both PPARα and PPARβ whereas PPARγ expression is almost restricted to this cell type suggest a significant role of PPAR-mediated regulation of cell function in melanomacrophages (Ibabe et al. 2004). By their diverse biological effects on cell proliferation and differentiation in the skin, PPAR agonists or antagonists may offer interesting opportunities for the treatment of various skin disorders characterized by inflammation, cell hyperproliferation, and aberrant differentiation (Di-Poi et al. 2004).

Of the synthetic ligands, the thiazolidinedione class of insulin-sensitizing drugs (ciglitazone, pioglitazone, troglitazone, rosiglitazone) is employed clinically in patients with type 2 diabetes (Zieleniak et al. 2008).

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