PPAR delta: an uncompletely known nuclear receptor

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SUMMARY
Peroxisome proliferator-activated receptors (PPAR) mediate some of the transcriptional effects of fatty acids and control many physiological functions, especially in the field of development and metabolism. Three isotypes are known, a, g and b/d. Roles of PPAR a and PPARgare now quite well-known, particularly since their pharmacologic ligands have been marketed, respectively the lipid-normalizing class of fibrates and the antidiabetic class of thiazolidinediones (glitazones). However, functions of PPARd are uncompletely known to date, but some recent data enlight its role in the regulation of fatty acid oxidation in several tissues, such as skeletal muscle and adipose tissue. Overexpression of PPARd using a transgenic murine model promotes an increase of muscle oxidative capability. This is accompanied by a redistribution of fatty acid flux, redirected from adipose tissue towards skeletal muscle. Finally, adipose mass is reduced, due to a decreased adipocyte size. These data strongly suggest that PPARd play a major role in the metabolic adaptations to western diet characterized by an excessive amount of saturated fat. Considering the metabolic properties of the two other PPAR isotypes, a and g it is likely that the three PPAR isotypes have complementary effects in the pathophysiology of obesity and metabolic syndrome. Future therapeutical perspectives in this field should consider combined treatment, adding g agonists (for all that their safety will be established) to the already available a and g agonists.

Key-words: PPAR · Diabetes · Metabolic syndrome · Atherosclerosis · Lipoprotein.

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 Peroxisome proliferator-activated receptors (PPARs) belong to the nuclear hormone receptor superfamily. Ligand activation heterodimerizes PPARs with another nuclear receptor, the 9-cis retinoic acid receptor, and this dimer acts on transcription of some target genes after binding to specific peroxisome proliferator response elements [1]. Three PPAR isotypes have been described, α, β/δ, and γ which differ by their target tissue and physiological properties [2]. PPARα is mainly found in liver. It is activated by polyunsaturated fatty acids and leukotriene B4, and this activation increases fatty acid catabolism. This explains the lipid-normalizing effect of fibrates, which are specific pharmacological activators. PPAR γ is expressed mainly in adipocytes, and is activated by prostaglandins and by thiazolidinediones (glitazones), a recently available class of insulin-sensitizing drugs. Functions of the third member of PPAR family, PPARδ, remained elusive until recently. Recent data using specific agonists and appropriate animal models have clarified its metabolic roles and enhanced the potential role of this receptor as a pharmacological target [3].

**PPARδ and regulation of lipid metabolism**

PPARδ has an ubiquitous tissue distribution: it is expressed in white adipose tissue, heart, muscle, intestine, placenta and macrophages [4]. It is activated by unsaturated or saturated long-chain fatty acids [5], by prostacyclin, by retinoic acid, and some eicosanoids [6] (Fig 1). Pharmacological agonists have been synthesized, especially GW 501516 and L 165041, which activate PPARδ with a much higher selectivity compared to other PPAR isotypes. A pivotal role of the synthetic specific agonist, GW 501516, has been evidenced by Oliver et al. In insulin-resistant obese rhesus monkeys, administration of GW 501516 during 4 weeks increased HDL-cholesterol, decreased LDL-cholesterol, triglycerides and fasting plasma insulin, and lowered the levels of small and dense LDL [7]. A major question was to identify the tissue and the mechanisms of action involved in these results. Administration of GW 501516 for 3 to 4 weeks in wild-type mice induces fatty acid β-oxidation in skeletal muscle [8]. Further evidence came from the utilization of transgenic murine models, which allowed tissue-specific overexpression of PPARδ. A ligand-independent active form of the nuclear receptor has been shown to be specifically expressed in white and brown adipose tissues, and it upregulated expression of genes involved in fatty acid catabolism and energy uncoupling in adipose cells [9]. This is accompanied by a decrease of adiposity in mice fed either with standard or high-fat diet. Using a transgenic mice model constructed with a Cre-Lox recombination technique, we showed that overexpression of PPARδ in skeletal muscle leads to a major increase of metabolic oxidative capability characterized by an elevated proportion of oxidative myofibers (type 2a) and elevation of oxidative enzymatic activities, accompanied by a dramatic reduction of body fat due to a decrease of adipocyte diameter [10]. The global result was a muscle remodelling characterized by an increase in the total number of oxidative fibers which is quite similar to that promoted by long-term moderate exercise. To challenge this hypothesis, we investigated the effects of endurance exercise on the PPARδ protein content in muscle of wild-type mice, and we showed that it was increased by 2.6 fold in tibialis anterior muscle after 6 weeks of training. Taken together, these results suggest that PPARδ is directly involved in the muscle remodelling observed during endurance exercise, and possibly in the beneficial effects of exercise on metabolic syndrome. Conversion of type 2 muscle fibers into type 1-like fibers has been also observed in mice overexpressing PPARδ-coactivator 1 (PGC-1) [11], but overexpression of PGC-1 is characterized by a complete conversion of fast-twitch into slow-twitch fibers, while overexpression of PPARδ does not promote appearance of actual type 1 fibers in tibialis anterior or plantaris muscles.

Mechanism of actions involves a redistribution of the non-esterified fatty acids (NEFA) flux: the increased oxidative capability draws the NEFA flux towards the muscle to be preferentially oxidized, rather than be stored in adipocytes. This leads to a decrease in adipocyte size, enhanced lipolysis and increased secretion of the main anti-atherogenic and insulin-sensitizing cytokine, adiponectin (Fig 3).

**PPARδ and atherosclerosis**

A growing body of evidence suggests that PPARδ could be involved in the pathophysiology of atherosclerosis due to its pivotal role in lipid metabolism. Implication of activation of the receptor in this field has been demonstrated by the previously cited study of Oliver et al. in obese rhesus monkeys [7]. Moreover some recent publications have focused on the possible link between polymorphisms of the PPARδ gene and the plasma concentrations of HDL- and LDL-cholesterol in various human populations. First, Skogsberg et al. showed that among four poly-
morphism (-409C/T, +73C/T, +255A/G, +294T/C), homozygote individuals for the rare C allele at the +294 locus had a higher plasma LDL-concentration than homozygotes for the common T allele [12]. Moreover, the same author, in individuals sampled from the prospective primary prevention West of Scotland Coronary Prevention Study, showed that individuals carrying the +294C allele had significantly lower plasma HDL-cholesterol concentrations compared to the carriers of the T-allele. Homozygous carriers of the C-allele also had a trend towards higher risk of coronary heart disease compared to the homozygous carriers of the T-allele [13]. Finally, Chen et al., in 372 individuals sampled from the Lipoprotein and Coronary Atherosclerosis Study, showed that PPARδ haplotypes were independent determinants of plasma levels of triglycerides, apoB and apoCIII, of mean number of coronary lesions, and of changes in triglyceride and apoCIII levels in response to a normolipidemic drug, fluvastatin [14]. Nevertheless, the effective role of PPARδ in atherosclerosis is still difficult to assess, as recent data have established both antiatherogenic and proatherogenic properties of the receptor. PPARδ seems to act as a VLDL sensor in macrophages and is therefore involved in lipid accumulation in atherosclerotic plaques [15]. Lee et al. have shown very recently that the role of PPARδ in inflammation depends whether a ligand is bound or not to

**Figure 1**

Physiological roles of PPAR δ. Different natural and synthetic ligands are known to activate this ubiquitous receptor. It is mainly involved in: a) regulation of development b) some pivotal metabolic regulations, as evidenced by Oliver et al. [7]. Exact mechanism and target tissues of this metabolic action remain partially unknown. LCFA: long chain fatty acid; PGI2: prostacyclin; HODE: hydroxyoctadecadienoic acid.

**Figure 2**

Integrated overview of the connecting action of PPARδ between muscle and adipose tissue. Activation of PPARδ either by ligands or exercise increases the amount of oxidative fibers in the muscle. This leads to a redistribution of the NEFA flux, then preferably directed to the muscle to be oxidized rather than stored by adipocytes. The resulting decrease in adipocyte size promotes secretion of the main anti-atherogenic cytokine, adiponectin. NEFA: non-esterified fatty acids.
the receptor. Binding leads to the release of B-cell lymphoma gene 6 (BCL-6), which is a repressor of inflammatory response; this results in decreased expression of inflammatory cytokine genes, reduced inflammation and subsequently possible decrease of atherosclerosis. Conversely, in the absence of ligand, BCL-6 remains bound to PPARγ, and the inflammatory process is no longer repressed [16]. These results show that the role of PPARγ in atherosclerosis is perhaps more ambiguous than previously thought.

Integrated roles of PPARs in the pathophysiology and treatment of metabolic syndrome

The metabolic syndrome is characterized by the simultaneous occurrence of at least three out of the five following metabolic disorders: hypertension, visceral adiposity, hyperglycemia, hypertriglyceridemia, low HDL-cholesterol levels [17]. The common soil of this cluster of cardio-vascular risk factors is an insulin resistance state. Each PPAR isotype can play a role in this syndrome [18]. The central role of PPARα has yet been demonstrated [19]. Its activation increases the uptake and catabolism of fatty acids, leading to a limited TG and VLDL production by the liver. It also inhibits the hepatic synthesis of ApoCIII, which is an inhibitor of lipoprotein lipase activity and remnant catabolism. Moreover, in reverse cholesterol transport from peripheral cells to liver, activation of PPARα induces synthesis of ApoA1 [20] and expression of the hepatic receptor SRB1 [21]. These changes are evidenced by the use of fibrates, which are specific pharmacological activators, leading to a decrease of plasma triglycerides concentration, and an increase of HDL-cholesterol plasma level. PPARγ plays also a major role in insulin resistance, by controlling adipogenesis [22]. Activation of PPARγ induces a remodelling of adipose tissue, with recruitment of new metabolically active adipocytes, promoting the secretion of an anti-atherogenic and insulin-sensitizing cytokine, adiponectin. A recently available class of pharmacological agonists of PPARγ, glitazones, displays not only hypoglycemic properties, but also a panel of pleiotropic actions, such as a decrease of C-reactive protein plasma level and expression of adhesion molecules and metalloproteinases, inhibition of proliferation of smooth muscle cells and secretion of numerous proatherogenic cytokines such as tumor-necrosis factor α and interleukin 6 [23]. Furthermore, glitazones increase adiponectin gene expression in adipose tissue and therefore plasma levels of this cytokine [24]. Antidiabetic actions of glitazones might also involve plasma NEFA-lowering effect through increased glycerol-3-phosphate availability for TG synthesis, by upregulation of phosphoenolpyruvate carboxykinase and glycerol kinase [25, 26]. Finally, the third isotype, PPARδ, seems to be greatly involved in the field. We have seen that utilization of an agonist of PPARδ is able in mice and monkeys to reverse the main features of the metabolic syndrome. Although level of experimental evidence is still restrained to animal model, clinical trials have been initiated in humans, and will provide important data concerning efficiency, tolerance and safety of the agonist.
Taken together, these data suggest that combined use of agonists of the three isotypes of PPARs (eventually combined in a “Poly-PPAR-Pill”, PPP) could target the whole body of pathophysiological features of the metabolic syndrome [27, 28](3).

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References