Review

MOLECULAR METABOLISM

Integrated physiology and systems biology of PPARα

Sander Kersten*

ABSTRACT

The Peroxisome Proliferator Activated Receptor alpha (PPARα) is a transcription factor that plays a major role in metabolic regulation. This review addresses the functional role of PPARα in intermediary metabolism and provides a detailed overview of metabolic genes targeted by PPARα, with a focus on liver. A distinction is made between the impact of PPARα on metabolism upon physiological, pharmacological, and nutritional activation. Low and high throughput gene expression analyses have allowed the creation of a comprehensive map illustrating the role of PPARα as master regulator of lipid metabolism via regulation of numerous genes. The map puts PPARα at the center of a regulatory hub impacting fatty acid uptake, fatty acid activation, intracellular fatty acid binding, mitochondrial and peroxisomal fatty acid oxidation, ketogenesis, triglyceride turnover, lipid droplet biology, gluconeogenesis, and bile synthesis/secretion. In addition, PPARα governs the expression of several secreted proteins that exert local and endocrine functions.

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Keywords PPARα; Liver; Transcriptional networks; Lipid metabolism; Expression profiling; Metabolic homeostasis; Systems biology

1. INTRODUCTION

PPARα was the first member to be cloned of a small subfamily of nuclear receptors called Peroxisome Proliferators Activated Receptors [1]. The other members of this subfamily are PPARδ, also referred to as PPARβ, and PPARγ [2]. Peroxisome proliferators encompass a diverse set of synthetic compounds that cause peroxisome proliferation and liver cancer in mice. Contradicting their name, PPARδ and PPARγ are not activated by peroxisome proliferators, in contrast to PPARα. The PPAR subfamily is part of the larger family of nuclear receptors that also includes receptors for fat soluble vitamins, steroid hormones, and sterols [3]. Nuclear receptors share a conserved modular structure consisting of a N-terminal domain involved in transcriptional activation, a DNA-binding domain containing a zinc-twist structure, a short hinge region, and a relatively spacious ligand binding domain, which accommodates the lipophilic ligands and also harbors a transcriptional activation function at the far C-terminus [4].

PPARs bind to DNA as a heterodimer with the Retinoid X Receptor RXR, and together they recognize specific DNA sequences in and around target genes referred to as PPAR response elements [5]. These PPAR response elements or PPREs consist of a direct repeat of the consensus hexanucleotide AGGTCA spaced by a single nucleotide. Agonist ligands for PPARs may promote the physical association of the PPAR–RXR heterodimer to DNA, but substantial binding of PPARs to DNA already occurs in the basal state [6]. In contrast to other nuclear receptor-RXR pairs, PPAR–RXR heterodimers are "permissive", which means that they can be activated by either an RXR-selective ligand ("rexinoid") or a PPAR ligand [7–9]. Binding of ligand leads to the dissociation of co-repressor proteins and the association of co-activator proteins, which can recruit or have intrinsic histone deacetylase and histone acetyltransferase activity, respectively, necessary for the assembly of the transcription initiation complex [10]. Readers are referred to another review for more detailed information on co-activators in PPAR-dependent gene regulation [11].

In addition to via direct binding to PPREs, PPARs and PPAR ligands also regulate gene expression by altering the activity of other transcription factors via direct protein–protein interactions. This action of PPARs generally inhibits the function of the other transcription factor and is referred to as transrepression. Transrepression predominantly accounts for the inhibitory effect of PPARs on inflammation related genes [12].

The most abundant natural ligands for PPARs encompass different types of (dietary) fatty acids and fatty-acid derived compounds, including various eicosanoids [13]. In addition, numerous dietary plant bioactive compounds have been suggested to serve as PPAR agonist, although the in vivo relevance of PPAR activation by these compounds remains uncertain. Finally, PPARs are the molecular target of different classes of drugs used in the treatment of diabetes and dyslipidemia.

All three PPARs are expressed in a variety of tissues [14,15]. Expression of PPARγ is most restrictive, showing high expression in white and brown adipocytes, macrophages and colonocytes, with lower expression in skeletal muscle and many other tissues. PPARδ is expressed in virtually all tissues and cell types examined, while expression of PPARα is highest in liver and brown adipose tissue, followed by small intestine, heart and kidney (http://biogps.org/). This review will concentrate on PPARα.

Since its discovery, PPARα has evolved from an intracellular receptor for synthetic peroxisome proliferators into one of the key transcriptional regulators of intermediary metabolism and an intermediate in the pathogenesis of numerous diseases [16]. Although most of our

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knowledge on PPARα is connected to its presence in the liver, studies on PPARα in other tissues, including heart [17,18], and small intestine [19] have indicated that the role of PPARα in metabolic homeostasis is relatively well conserved between different cell types. The first part of this review addresses the role of PPARα in intermediary metabolism in liver. A distinction is made between the metabolic function of PPARα upon physiological, pharmacological, and nutritional PPARα activation. As a transcription factor, PPARα governs biological processes by altering the expression of numerous target genes. Accordingly, the functional role of PPARα is directly related to the biological function of its target genes. In the second part of the review, a comprehensive overview is provided of metabolic genes targeted by PPARα, organized into specific metabolic pathways.

2. REGULATION OF INTERMEDIARY METABOLISM BY PPARα UPON PHYSIOLOGICAL, NUTRITIONAL AND PHARMACOLOGICAL ACTIVATION

2.1. Physiological PPARα activation during fasting

2.1.1. Regulation of the adaptive response to fasting by PPARα

Throughout our ancestral history, fasting and starvation were common occurrences that posed a major threat to the survival of the human species. As a consequence, humans have developed an adaptive response mechanism to fasting that relies on two main pillars: 1) generation of a strong hunger sensation that triggers food-seeking behavior and 2) a shift in fuel utilization to exploit the abundant triglyceride stores in the adipose depot. A key event during fasting is activation of adipose tissue lipolysis, contributing to a gradual shift in whole-body fuel utilization from glucose and fatty acids in the fed state to almost exclusively fatty acids after a day of fasting [20]. The shift in fuel utilization is governed by changes in the production of the metabolic hormones insulin and glucagon, as well as by altered secretion of several gut- and adipose-tissue derived hormones. Within this complex network of metabolic adjustments, the liver plays a key role through its exclusive ability to synthesize glucose and catalyze the formation of ketone bodies [20]. Ample provision of glucose and ketone bodies is necessary to meet the needs of the metabolically active brain, which unlike other tissues and organs is unable to utilize fatty acids as fuel. Research in the past two decades has shown that PPARα is a master regulator of hepatic nutrient metabolism during fasting [21–23]. Specifically, PPARα induces hepatic fatty acid oxidation and ketogenesis and regulates hepatic glucose production, which are key events in the adaptive response to fasting (Figure 1). Additionally, PPARα governs hepatic amino acid metabolism. Elucidation of the role of PPARα during fasting has benefited immensely from the availability of PPARα−/− mice, which exhibit a striking fasting-induced phenotype [21–23].

2.1.2. Regulation of hepatic lipid homeostasis during fasting by PPARα

As indicated above, a crucial event during fasting is activation of adipose tissue lipolysis, resulting in elevated circulating levels of glycerol and free fatty acids (FFA) and elevated flux of fatty acids into many tissues including liver. Increased hepatic uptake of fatty acids during fasting is associated with activation of a number of pathways, most prominently the activation of hepatic fatty acid oxidation and concomitant production of ketone bodies (Figure 2A). Metabolic data have unequivocally demonstrated the crucial role of PPARα in stimulation of hepatic fatty acid oxidation and ketogenesis during fasting [21–25]. Indeed, the increase in plasma ketone body levels during fasting is largely abolished in fasted mice lacking PPARα [26] (Figure 2B, Table 1), which is caused by blunted fasting-induced upregulation of numerous PPARα target genes involved in fatty acid oxidation (e.g. Cpt1a, Cpt2, Acadvl, Hadha) and ketogenesis (Hmgcs2, Hmgcl, Acat1). Furthermore, plasma levels of long chain acyl-carnitines are increased in fasted PPARα−/− mice, whereas plasma levels of medium and short chain acyl-carnitines and free carnitine are decreased, reflecting impaired fatty acid oxidation (Table 1) [21,27]. Decreased rates of hepatic fatty acid oxidation and

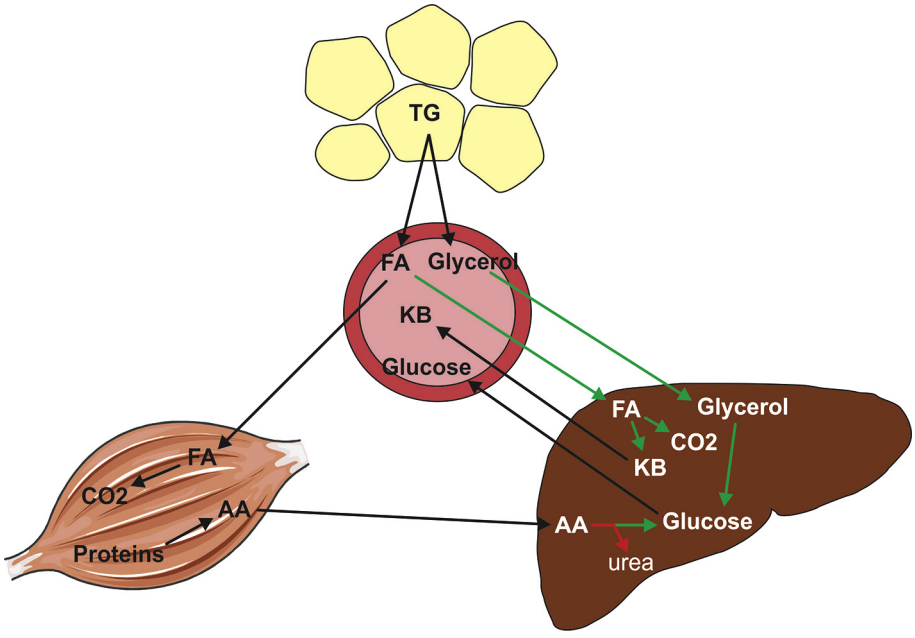

Figure 1: Overall role of PPARα in the adaptive response to fasting. Fasting is associated with activation of adipose tissue lipolysis, leading to the release of free fatty acids and glycerol into the circulation. Free fatty acids taken up by the liver are partially oxidized and converted into ketone bodies, or completely oxidized to CO_2. Glycerol is converted into glucose, as are amino acids coming from skeletal muscle. The processes induced by PPARα are indicated by green arrows. The processes suppressed by PPARα are indicated by red arrow. TG = triglycerides, FA = fatty acids, KB = ketone bodies, AA = amino acids.

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