

Revisión

Peroxisome proliferator-activated receptor: effects on nutritional homeostasis, obesity and diabetes mellitus

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Abstract

The obesity and the metabolic disorders associated characterize the metabolic syndrome, which has increased at an alarming rate around the world. It is known that environmental and genetic factors are involved in the genesis of obesity. Peroxisome Proliferator-Activated Receptors (PPARs) stand out among these factors. They compose the nuclear receptor superfamily and there are in three isoforms (PPAR α , PPAR β/δ and PPAR γ), which play an important role in the regulation of the metabolism of carbohydrates, lipids and proteins. The present review aims to understand the relationship between the diet, the PPARs and the control of the blood glucose and body weight, since the understanding about the mechanisms by which these receptors act may benefit the development of the strategies aiming at prevention and elaboration of therapeutics actions which are more effective for the treatment of obesity and diabetes.

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Key words: *Peroxisome Proliferator-Activated Receptors. Obesity. Diabetes Mellitus. Metabolism.*

RECEPTORES ACTIVADOS POR LOS PROLIFERADORES DE PEROXISOMAS: IMPLICACIONES SOBRE LA HOMEOSTASIS NUTRICIONAL, EN LA OBESIDAD Y EN LA DIABETES MELLITUS

Resumen

La obesidad y los trastornos metabólicos asociados, que caracterizan el cuadro del síndrome metabólico, han aumentado de manera alarmante en todo el mundo. Se sabe que factores genéticos y ambientales están implicados en la génesis de la obesidad. Entre estos se destacan los Receptores Activados por los Proliferadores de Peroxisomas (PPAR), los cuales componen la superfamilia de los receptores nucleares que poseen tres isoformas de PPAR (PPAR α , PPAR β/δ y PPAR γ) que desempeñan importante papel en la regulación del metabolismo de los hidratos de carbono, de los lípidos y de las proteínas. El presente trabajo de revisión contribuye a clarificar la interrelación existente entre la dieta, los PPAR y el control de la glucemia y peso, ya que el conocimiento de los mecanismos por los cuales estos receptores actúan, puede beneficiar el desarrollo de estrategias de prevención y elaboración de procedimientos terapéuticos más eficaces para el tratamiento de la obesidad y de la diabetes

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Palabras clave: *Receptores activados por los proliferadores de peroxisomas. Obesidad. Diabetes mellitus. Metabolismo.*

Abbreviations

PPARs: Peroxisome Proliferator-Activated Receptors.

DM2: type 2 diabetes.

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MS: Metabolic Syndrome
BMI: Body Mass Index
FABPs: fatty acid binding proteins
LCFAs: long chain fatty acids
FAT: fatty acid translocase
VLDL: very low density lipoprotein
FATPs: fatty acid transport proteins
PPAR^{-/-}: rat deficient in PPAR
AOX^{-/-}: rat deficient in acyl-CoA oxidase
CPT 1: carnitine palmitoyl transferase-1
MCAD: acyl-CoA dehydrogenase
mHMG-CoAS: hydroxymethylglutaryl-CoA synthase.

NADPH: nicotinamide adenine dinucleotide phosphate.

LDLs: low density lipoproteins.

DCV: cardiovascular diseases.

LPL: peripheral lipoprotein lipase.

VCAM-1: vascular cell adhesion molecule-1.

HDL: high density lipoprotein.

Pref-1: pre-adipocyte marker.

aP2: fatty acid binding protein in the adipocyte.

PUFA: polyunsaturated fatty acids.

SCD 1: stearoyl CoA desaturase-1.

TZD: troglitazone.

GLUT4: insulin-dependent glucose transporter.

Introduction

Obesity is an endocrine disease characterized by excessive accumulation of adipose tissue, whose occurrence and implications result from the body's inability to maintain energy balance.¹ This disease is associated to clinical disorders (insulin resistance, type 2 diabetes-DM2, dyslipidemia, hypertension and cardiovascular diseases), involving environmental, genetic and nutritional factors, which, together, determine the Metabolic Syndrome (MS).

Peroxisome proliferator-activated receptors (PPARs) are among the processes which allow the adaptation of metabolic and functional responses to extracellular signs. Scientific evidence suggests that PPAR can be focused in treatments potentially effective against MS, once it seems that there is a relation between the role played by these receptors and MS.² The present review aims to describe the molecular mechanisms involved in the activity of the PPARs family on the metabolism of lipids, carbohydrates and proteins, and their effect on obesity and diabetes.

PPAR: characteristics and forms of activation

Expressed in three isoforms (PPAR α , β/δ and γ), the PPARs are nuclear receptors that belong to the family of transcription factors, whose functions are similar to those of steroid receptors, and are related to the multiple functions started by nutrients, nutraceuticals and phytochemicals.^{1,3}

The effects of the activity of relatively slow PPARs can be achieved by means of the action of ligands which comprise a variety of natural lipophilic compounds, such as polyunsaturated fatty acids; arachidonic acid metabolites; byproducts of oxidized lipoproteins and synthetic ligands, such as fibrates and thiazolidinediones.^{2,4,5}

Fast responses related to the transcription of genes modulated by PPAR may occur by means of the phosphorylation of these receptors, which start to work independently. It is considered that it is generated a new conformation that allows the transcriptional regulation of the target-gene.⁶

PPAR α , PPAR β/δ and PPAR γ expression and regulation

In humans, PPAR α are expressed mainly in the liver, heart, skeletal muscle, kidney and small intestine. They are present in important mechanisms, such as the capture and oxidation of fatty acids; synthesis of ketone bodies; metabolism of apolipoproteins (apoAI and apoAII); expression of genes involved in gluconeogenesis; inhibition of transamination and deamination of amino acids, as well as the blocking of urea synthesis.⁶

In rat liver, the PPAR α expression is subject to the negative or positive regulation by insulin or glucocorticoids, respectively. The concentrations of PPAR α mRNA and the receptor itself are affected by the circadian rhythm of circulating glucocorticoids. Stressful situations that elevate these hormones also contribute to increased PPAR α in hepatocytes. In contrast, exposure of a culture of rat hepatocytes to growth hormone may lead to 50% decrease in PPAR α mRNA, which leads to reduced β -oxidation induced by PPAR α .⁷

In humans, PPAR β/δ is widely distributed in the tissues and is expressed in the placenta and small intestine. The mechanisms involving the gene expression regulation of this receptor are unknown, but it is an important agonist in the treatment of dyslipidemia and cancer and acts in the differentiation of central nervous system cells.⁸

PPAR γ is abundant in adipose tissue and is present in low concentrations in the skeletal muscle of humans. As a receptor of antidiabetic drugs (troglitazone and rosiglitazone), it leads to increased sensitivity to insulin in the adipose and muscle tissues, by improving glucose metabolism; reduces inflammation and promotes the differentiation of pre-adipocytes in adipocytes.^{6,9}

The regulation of the PPAR γ expression has been studied under *in vivo* and *in vitro* conditions. Vidal-Puig et al. (1997)¹⁰ investigated the PPAR expression in the subcutaneous adipose tissue of thin and obese individuals. The study revealed that the adipose tissue of obese people presents an increased amount of PPAR γ 2 mRNA. Besides, an increased PPAR γ 2/PPAR γ 1 ratio was observed in relation to the Body Mass Index (BMI). By eating low-calorie diet, the overweight individuals presented reduced PPAR γ 2 expression. A research work involving obese individuals concluded that the PPAR γ 1 mRNA levels in the abdominal subcutaneous adipose tissue did not correlate with BMI.¹¹ Such hypotheses help understand the molecular mechanisms which may lead to obesity by means of the activation of different PPAR γ isoforms and, in this case, it seems that the isoform 2 is the most active in adipogenesis.

The PPAR γ expression was also assessed in muscle tissue and cell culture of thin, nondiabetic obese and type 2 diabetic individuals. It was observed increased PPAR γ (1 and 2) both in nondiabetic obese and type 2 diabetic individuals and they correlated with the BMI and fasting insulin.¹² It suggests that increased concen-

tration of PPAR γ may correlate with the insulin resistance of the skeletal muscle related to obesity and diabetes.

PPAR and its influence on nutrient metabolism

The metabolic destination of diet macronutrients is regulated by the need of organisms for synthesizing essential cell components; providing fuel energy for vital metabolic processes and; storing carbon, primarily in the form of lipids, to be used for future needs.¹³ Mechanisms associated to fat accumulation and the complications related to it have been investigated, mainly the PPARs functions.

PPAR and lipid metabolism

PPAR participates in the transcriptional control of genes that codify proteins involved in important metabolic steps of fat metabolism and energy homeostasis, such as the transport of fatty acids and their capture by cells, intracellular binding and activation, as well as catabolism (β -oxidation and ω -oxidation) or storage (table I).⁷

PPAR in the digestive tract

The triglycerides and phospholipids found in a diet are absorbed mainly in the jejunum and duodenum, while the cholesterol is absorbed mainly in the ileum. In these intestinal regions, the high expression of PPAR α and PPAR β/δ is correlated to the concentration of fatty acid binding proteins (FABPs) in enterocytes: FABP-I and FABP-L. A strongly positive regulation of the FABP-L genes is observed with the intake of diets rich in long chain fatty acids (LCFAs) or with indirect infusion of linoleic acid or α -bromopalmitate (PPAR α and PPAR β/δ ligands).^{14,15,16} This datum suggests a relation between PPAR and the expression of FABP in the intestine.

Another gene activated by these PPAR is that of fatty acid translocase (FAT), which seems to facilitate the transport of LCFA into the enterocyte. Genes involved in the incorporation of the LCFA in triglycerides and their introduction in the chylomicrons or very low density lipoprotein (VLDL), as well as those which encode acyl-CoA synthase (ACS) or apolipoproteins, are also activated by PPAR.⁷ Therefore, it is evident that PPARs are indirectly involved in the first stages of absorption and transport of lipids in the organism.

PPAR α in the liver

The stages of the transport of fatty acids through the cell membrane and the activation of acyl-CoA, necessary for lipid metabolism, are facilitated by the synthesis of fatty acid transport proteins (FATP), by PPAR α . The formation of lipids by acyl-CoA precedes their incorporation in triglycerides (anabolism) or their oxidation (catabolism) by two main pathways, peroxisomal β -oxidation and mitochondrial β -oxidation. In each of these pathways, the expression of some key enzymes is stimulated by PPAR α .^{7,8}

PPAR α : peroxisomal and mitochondrial β -oxidation

The genes activated by PPAR α codify peroxisomal β -oxidation enzymes, such as acyl-CoA oxidase, which is limiting to this pathway; enoyl-CoA hydratase/dehydrogenase, multifunctional enzyme; and keto-acyl-CoA thiolase. Besides, the action of PPARs has been observed on the regulation of enzymes contained in peroxisomes, involved in the cholesterol synthesis.¹⁷

In rats deficient in PPAR α (PPAR $\alpha^{-/-}$) and, or in acyl-CoA oxidase (AOX $^{-/-}$), it is demonstrated that these molecules are vital for the peroxisomal oxidation and prevention of hepatic steatosis.¹⁸

The function of PPAR α in energy homeostasis is also related to the regulation of the mitochondrial β -oxidation. The first limiting step of this process is the influx of fatty acids into the mitochondria, which is favored

Table I
Mechanisms regulated by PPARs: lipid metabolism

<i>Gut</i>	– PPAR α and PPAR β/δ are indirectly involved in the first stages of absorption and transport of lipids in the organism.
<i>Liver</i>	– PPAR α stimulates the lipids elimination by means of peroxisomal and mitochondrial oxidation, as an attempt to avoid lipotoxicity. – Pathways activated by PPAR α favor their transport for the tissues.
<i>Bloodstream</i>	– PPAR α can participate in routes which favor to lipid removal from circulation, as well as in mechanisms which reduce the expression of vascular adhesion molecules.
<i>Adipose tissue</i>	– PPAR α increases the mRNA levels of genes which express the enzymes involved in capture of lipids by adipocytes and by peroxisomal and mitochondrial β -oxidation. These proteins may be related with the decrease of the fat deposits and improvement of the sensitivity to insulin. – PPAR γ induces the differentiation of pre-adipocytes in mature fat cells, the activation of genes involved in lipogenesis and storage of triglycerides.

by the carnitine palmitoyl transferase-1 (CPT 1), whose expression is strongly induced by PPAR α .¹⁹ Minnich *et al.* (2001)²⁰ demonstrated that, after three days, the CPT 1 expression increased in the liver of hamsters fed a hyperlipid diet and treated with ureidofibrate-5. After three weeks of treatment, the increase of CPT 1 was also observed in the muscle, which contributed for the reduction in plasma lipids. This nuclear receptor also seems to regulate the mitochondrial β -oxidation by modeling the gene expression of acyl-CoA dehydrogenase (MCAD), the enzyme which oxidates acyl-CoA.¹⁹

As observed in fast or diabetes, much of acetyl-CoA is converted into ketone bodies, mainly acetoacetate and β -hydroxybutyrate. The mitochondrial hydroxymethylglutaryl-CoA synthase (mHMG-CoAS) is the main enzyme involved in the formation of ketone bodies and is directly controlled by PPAR α . Under *in vivo* conditions, in the presence of PPAR α , mHMG-CoAS is carried to the nucleus, where its own PPAR α -dependent gene transcription is potentiated.⁷

Thus, the lipids present in the liver stimulate, via PPAR α , its elimination by means of peroxisomal and mitochondrial oxidation, as an attempt to avoid lipotoxicity.

PPAR α and fatty acid synthesis

It has been suggested that PPAR α can work as a sensor of the supply of tissue lipids by regulating their capture and oxidation, in opposition to the function of PPAR γ , which promotes the capture and subsequent storage of lipids in the adipose tissue.²¹

The hypothesis of the involvement of PPAR α in the fatty acid synthesis started with the demonstration that the malic enzyme gene is activated by PPAR α . Nicotinamide adenine dinucleotide phosphate (NADPH), which is necessary for lipid synthesis, is one of the products of the reaction catalyzed by this enzyme. It must be also considered that the activation of the malic enzyme gene increases the amount of pyruvate, one of the main metabolites related to lipid synthesis.⁷ Therefore, in addition to β -oxidation, and to avoid the accumulation of lipids in the liver, pathways activated by PPAR α favor their transport for the tissues.

PPAR α in the cholesterol and lipoprotein metabolism

Since diets are the main source of cholesterol, Knight *et al.* (2003)²² studied the effect of WY 14643 (agonist of PPAR α) on wild rats and PPAR α ^{-/-} and found reduced intestinal absorption of cholesterol in the wild rats, which also resulted in cholesterol decreased concentration in the plasma and liver.

As for the metabolism of lipoproteins, it is well established that high concentrations of low density lipoproteins (LDLs) is a risk factor for cardiovascular

diseases (DCV). Small and dense LDL have properties of adherence and retention in the arterial wall, which increase the susceptibility to oxidation and, consequently, DCV risk⁷. The pathway that allows the formation of LDL starts in the synthesis of VLDL in the liver and its release in the bloodstream. This particle has its triglycerides hydrolyzed when in contact with the peripheral lipoprotein lipase (LPL) placed on the endothelium. Lipid products derived from this process can activate the PPAR α expressed in peripheral tissues, culminating with the reduced atherogenic events. This is due to the fact that these receptors regulate the expression of genes such as that of the vascular cell adhesion molecule-1 (VCAM-1). Besides, PPAR α favor the increased SR-BI expression (receptor "scavenger") in the liver, which is responsible for the capture of cholesterol, and consequent degradation of atherogenic particles. PPAR α activation also inhibits the expression of apo CIII, which works as a suppressor of the LPL activity.²³

Therefore, PPAR α s seem to perform their functions in the initial pathways of the cholesterol and lipoprotein metabolism. When activated, these receptors can participate in routes which favor lipid removal from circulation, which implies in shorter period for the formation of atherogenic particles, as well as in mechanisms which reduce the expression of vascular adhesion molecules.

A process similar to that of the activation of PPAR α by metabolites from the VLDL hydrolysis occurs when products from the degradation of the high density lipoprotein (HDL) resulting from the activity of the endothelial lipase activate this receptor. Consequently, it starts the expression of genes that codify proteins involved in the lipid efflux, such as that of the apoAI, which works in the first step of the reverse cholesterol transport.²³ Thus, the participation of PPAR α in the HDL metabolism may possibly explain the anti-inflammatory effects credited to this lipoprotein.

PPAR α and adiposity

Evidences suggest that there is a relation between PPAR α and the adipose tissue function. Rats and mice fed lipid-rich diets and synthetic PPAR α activators reduced adiposity.⁸ Cabrero *et al.* (2001)²⁴ studied the exposure of rat adipose cell culture to bezafibrate, an PPAR α activator, and verified increased concentrations of mRNA of genes which express enzymes involved in peroxisomal and mitochondrial β -oxidation. Besides, bezafibrate increased the mRNA levels of the fatty acid translocase, suggesting an increased capture of lipids by adipocytes. The concentrations of mRNA of fatty acid binding proteins also increased, indicating the mobilization of lipids to the mitochondria and peroxisomes. This agonist also reduced the mRNA expression of many adiposity markers, including the one of PPAR γ . Along with such decrease, there was an increased concentration of

mRNA of the pre-adipocyte marker (Pref-1). These changes in the concentrations of these markers may be related to reduced fat deposits and improved insulin sensitivity.

PPAR γ and adipogenesis

It is known that the adipose tissue function changes in obese individuals presenting insulin resistance and other factors which characterize the metabolic syndrome, in whom morphological changes are observed in adipocytes (increased size), associated to hyperglycemia, indicating the beginning of DM2.²⁵

The great interest of researches in investigating PPAR γ is not only due to its high level of expression in the adipose tissue, but also its important role in adipogenesis.²⁶ This was demonstrated in lineages of pre-adipose cells which express small amounts of this receptor. The occurrence of PPAR γ during differentiation induced the adipose phenotype, which is defined by the accumulation of lipids and the gene expression related to this process, such as that of the fatty acid binding protein in the adipocyte (aP2), LPL and adpsin. Under *in vitro* conditions, PPAR γ also induced the differentiation of pre-adipocytes in mature fat cells of the human subcutaneous adipose tissue, together with the activation of genes involved in lipogenesis and storage of triglycerides.²⁵

PPAR γ and lipogenesis

The effect of PPAR γ on the accumulation of lipids in adipocytes is unknown, but it is suggested that this receptor can exert an important role in lipogenesis regulation. In the attempt to understand this mechanism, Kubota *et al.* (1999)²⁷ studied heterozygous PPAR γ deficient mice, fed hyperlipid-rich diet, and verified that these animals presented lower weight gain and less adipose tissue, when compared to the control group.

The genes which are under the transcriptional control of PPAR γ in the adipose tissue include the codifiers of enzymes involved in fatty acid metabolism, such as LPL, acyl-CoA synthetase, FAT-CD36 and FATP. It suggests that PPAR γ plays an important role in lipid capture by adipocytes.²⁶ The synthesis of fatty acids and triglycerides in enterocytes occurs similarly as in hepatocytes. In other words, it is promoted by the activation of the gene of the malic enzyme mediated by this receptor.⁷

Way *et al.* (2001)²⁸ investigated the effects of GW 1929 (PPAR γ agonist) on concentrations of glucose and triglycerides and the gene expression in diabetic and obese Zucker rats. This work aimed at verifying the molecular mechanisms employed by the drugs that increase sensitivity to insulin and reduce the concentrations of glucose and triglycerides in individuals with DM2. The authors observed that the treatment

reduced the concentration of free fatty acids after decreasing the concentrations of glucose and triglycerides. Besides, it was observed an increased expression of genes present in the adipose tissue, mainly some involved in lipogenesis, such as acetyl-CoA carboxylase, fatty acid synthase and ATP-citrate lyase. Genes involved in lipid oxidation were also stimulated by GW 1929, which probably occurred due to the interaction of this compound with PPAR α present in the liver.

In spite of participating of gene activation, PPAR γ can act in the inhibition of others, such as the one which codifies leptin, a hormone that inhibits food intake and stimulates energy expenditure by the activation of lipolysis and oxidation of fatty acids.^{8,29} Paradoxically, the expression of PPAR γ and leptin is reduced by fasting and increased by food intake. In the last case, PPAR γ can attenuate the increase of this hormone aiming at limiting lipolysis and lipid oxidation.⁸

Kadowaki *et al.* (2003)³⁰ investigated the PPAR γ expression and the concentration of leptin in mice with and without deficiency of this receptor, which consumed fat-rich diet. The authors observed that the leptin expression was slightly increased in the control group, while the PPAR γ deficient group presented a strong increase in this hormone. Besides, the adipocytes of the animals were smaller than those in the control group, as well as the mass of white adipose tissue. Such results indicate that PPAR γ regulates obesity and insulin resistance induced by the hyperlipid diet, partly due to the decreased leptin, which, by stimulating lipolysis, hinders the capture of insulin-mediated glucose.

At molecular level, the role of polymorphic transcription factors was exemplified by the relation between the regulation of their functions and the occurrence of metabolic changes caused by the modification of the type of fat ingested. Rosado *et al.* (2006)³¹ evaluated obese women, with polymorphisms to PPAR γ 2 and β 2-adrenergic receptors, which consumed hypocaloric diet with different types of lipids. It was verified that the intake of polyunsaturated fatty acids (PUFA) by the women with both polymorphisms produced higher lipid oxidation, without reducing the basal metabolism. The same was not observed for those with polymorphism in the β 2-adrenergic receptor only. The polymorphism in PPAR γ 2 associated to PUFA intake favored weight loss, corroborating the functional changes of the gene. Thus, it was concluded that the polymorphism in the gene PPAR γ 2, regardless of β 2-adrenergic, leads to higher lipid oxidation, which may affect the content of body fat. On the other hand, according to Jeffcoat (2007),¹³ PUFA by themselves could contribute for the reduction in body weight because they inhibit the activity of the enzyme stearoyl CoA desaturase-1 (SCD 1), which catalyzes the formation of monounsaturated fatty acids necessary for triglyceride synthesis. Thus, the type of lipid ingested seems to affect different pathways involved in weight gain, but it is still unknown if the results are additional or synergistic.

Table II
Relationship between PPARs and carbohydrate metabolism

<i>PPARα</i>	– Exposure of β cells to high glucose levels leads to reduction of the mRNA coder of the PPAR α what favor the accelerated deposition of the fatty acids.
<i>PPARβ/δ</i>	– Improvement of the hyperglycemia. – Increase of the insulin activity.
<i>PPARγ</i>	– Controls the glucose levels and favors the increase of the sensitivity to insulin in DM2 patients.

Effect of high lipid intake: PPAR and insulin resistance

It is observed that the consumption of fat-rich diets, in a long run, is the main cause of obesity and insulin resistance.³⁰ Adipogenesis induction associated to the ability to capture fatty acids has proved to be an important element in the maintenance of systemic insulin sensitivity.³²

It seems that fatty acid oxidation related to increased PPAR α may reverse hepatic insulin resistance, which was observed in essays with animal models, fed saturated-fat-rich diet.³³ However, *knockout* mice for PPAR α seem to be protected against insulin resistance induced by hyperlipid diet, probably due to increased adiposity caused by the absence of PPAR α .³⁴ The *in vivo* treatment with WY14643 (agonist of PPAR α) for 24 hours reversed insulin hypersecretion without affecting glucose tolerance, which suggests that the improvement in insulin activity reduced the need for the compensatory secretion of this hormone.³⁵

Okuno et al. (1998)³⁶ investigated the effect of the troglitazone (TZD) treatment applied to Zucker rats on the stimulation of PPAR γ . It resulted in increased number of small adipocytes and reduced number of large adipocytes, which produced TNF α and free fat acids and led to insulin resistance. These data demonstrate that the stimulation of PPAR γ increases the number of small adipocytes, through differentiation, thus enhancing insulin resistance. However, it is considered that the differentiation of adipocytes does not often occur in adult life and the induction of this process by TZD is a physiological event.

It was developed a model of PPAR $\gamma^{+/-}$ mouse, which was used by Kubota et al. (1999)²⁷ aiming at elucidating the physiological role of PPAR γ . These animals were fed fat-rich diet for 15 weeks, and the authors discovered that this animal model was protected against the development of insulin resistance due to adipocyte hypertrophy. Amazingly, the insulin activity, reducing the concentrations of glucose, was more efficient in these mice, in comparison with those in the control groups, which indicates that these animals are more sensitive to insulin. Trying to understand these data, it was observed that the intake and weight gain of the PPAR $\gamma^{+/-}$ mice was lower, compared to the animals in the control groups. Besides, the rectal temperature was higher in the deficient mice, demonstrating that their energy expenditure was higher. Therefore, the results suggest that PPAR γ regulates obesity, induced by

hyperlipid diet, adipocyte hypertrophy and insulin resistance.

PPAR and carbohydrate metabolism

In the case of other pathways regulated by nutrients, glucose is both final product and substrate/nutrient, responsible for modulating gene transcription via PPAR (table II).

PPAR α seems to affect carbohydrate metabolism by means of compensatory insulin secretion by the Islets of Langerhans, influencing glucose regulation and lipid regulation. The chronic exposure of the Islets of Langerhans to high concentrations of glucose hinders their activity. Lipotoxicity and glucotoxicity present several common characteristics because the metabolism of lipids and carbohydrates are closely related, since these substrates act as competitors.^{21,37}

The greatest problems are observed when the concentrations of glucose and lipids are concomitantly high. The combination of excessive glucose and fatty acids may result in their deviation from β -oxidation to the formation of extra-mitochondrial signaling metabolites, which started to change insulin secretion.²¹

Effect of the PPAR signaling on insulin secretion and activity

The effects of glucose on the Islets of Langerhans are not only intense but also long-lasting. A glucose optimal concentration is necessary to maintain the competence related to insulin secretion. Chronic exposure to low (< 6 mmol/L) or high (> 20 mmol/L) glucose concentrations is fundamental for insulin secretion in response to acute stimulation. Particularly, the exposure of β cells to high glucose levels (above physiological levels) for several days leads to a reduction of approximately 60% to 80% in the PPAR α mRNA expression. This is related to the decreased expression of acyl-CoA dehydrogenase mRNA, which catalyzes the rate-limiting step of the peroxisomal β -oxidation and the uncoupling protein 2, which is important for the uncoupling of the mitochondrial lipid oxidation, thus favoring the accelerated fatty acid deposition. Consequently, the chronic exposure to high glucose concentrations affects the β cell lipid metabolism, reducing the oxidation capacity related to PPAR α .²¹

According to a study carried out by Sugden et al. (2002),³⁸ although the glucose concentrations in the plateau are similar, insulin concentration is 2 times higher in the 24-hour fasting in *knockout* mice for PPAR α , in comparison to the control. This observation leads to the conclusion that the absence of signaling via PPAR α is possibly caused by the inhibition of lipid degradation via oxidation, increasing insulin secretion until the achievement of basal glucose concentrations in fasting conditions.

The activation of PPAR β/δ by specific agonists in animal models (PPAR $\beta/\delta^{-/-}$ mice and *db/db* mice) seems to improve hyperglycemia by increasing carbohydrate hepatic catabolism, suppressing glucose capture in the liver and promoting lipid β -oxidation in muscles. Therefore, PPAR β/δ may contribute to the regulation of the metabolic homeostasis and increase insulin activity in a complementary way in different tissues.³⁹

PPAR and agonists in tissue sensitization to insulin

PPAR γ activation by means of its synthetic ligands, such as TZD, results in strong improvement in the concentrations of glucose and insulin in DM2 patients. The PPAR γ activity in different tissues (adipose, skeletal muscle and liver) as mediator of glucose homeostasis and insulin homeostasis is still unknown. However, two mechanisms are proposed: 1) the PPAR γ present in the adipose tissue protects the liver and muscle against lipid overload; and 2) PPAR γ in the adipose tissue ensures the balance and adequate production of adipokine, such as leptin, an important mediator of the insulin activity in peripheral tissues.³²

Wu et al. (1998)⁴⁰ demonstrated that the expression of the gene that codifies the insulin-dependent glucose transporter (GLUT4) is activated by PPAR γ and TZD, in the adipose tissue. The effect of PPAR γ on the adipose tissue is considered the main mechanism through which the TZD improves insulin sensitivity in patients resistant to this hormone. In some patients, the TZD are hypolipidemic and hypoglycemic agents. A mechanism proposed to explain the improvement in insulin sensitivity would be the capture of fatty acids and *clearance* of triglycerides, which would redirect the fatty acids from the muscle to the adipose tissue and would then minimize the inhibition of the use of the glucose mediated by fatty acids in muscle cells. Besides, the PPAR γ present in the adipose tissue may stimulate the production and secretion of regulatory molecules of the route of insulin signaling in muscles and liver.⁷

Way et al. (2001)²⁸ verified that the activation of PPAR γ stimulated the expression of genes involved in the lipogenesis and metabolism of fatty acids both in the white and brown adipose tissue. In the muscle, the treatment with PPAR γ agonist decreased the expression of the protein PDK4, which inhibits the glucose

oxidative metabolism and the expression of genes involved in the transport and oxidation of fatty acids. According to the authors, these changes suggest the molecular base for the increased use of the glucose mediated by PPAR γ in the muscle. In the liver, it increases the expression of genes involved in the gluconeogenesis. Thus, the antidiabetic activity of PPAR γ agonists is due to their effects on the capture and oxidation of fatty acids in the muscle, which favors insulin sensitivity increase.

PPAR and protein metabolism

The effect of PPAR and its agonists on the metabolism of lipids and carbohydrates has already been demonstrated, but little is known about their effects on the metabolism of amino acids.

Kersten et al. (2001),⁸ comparing the liver RNA of wild mice and of mice with deletions to PPAR α , found that this type of PPAR reduces the mRNA expression of enzymes involved in the metabolism of amino acids in fasting conditions. They also verified that the PPAR α affects the expression of several genes involved in the trans- and deamination of amino acids and urea synthesis. The activation of PPAR α , with the use of its analogous WY14643, in the fed state, decreased the mRNA concentration of these genes in wild mice, suggesting that PPAR α is directly involved in the regulation of their expression. The authors concluded that, in addition to lipid metabolism, the PPAR α s also regulate the protein metabolism in the liver.⁸

Sheikh et al. (2007)⁴¹ investigated the response of the PPAR α agonist, WY14643, in rats fed saturated fat rich diet, which were divided into two groups: an untreated group and a group treated with WY14643. They observed that the treated group presented reduced insulin resistance and dyslipidemia. Besides, the treatment reduced the weight gain, without changing food intake. WY14643 increased the plasma concentrations of 12, out of the 22 amino acids, including glucogenic and ketogenic. Arginine was reduced, while the amino acids of the branched-chain remained unchanged. The study demonstrated that the pharmacological effects of the PPAR activation in rodents not only control the lipid metabolism, but also strongly affect the mobilization of body amino acids and metabolization by the liver.

In a review study, Sugden and Holness (2004)²¹ inferred that PPAR α activation could suppress the degradation of amino acids in the Islets of Langerhans. According to the authors, the absence of signaling via PPAR α in the Islets, in fast, seems to contribute for increased insulin secretion stimulated by amino acids in *knockout* mice for PPAR α .

Although little is known about the PPAR actions on the metabolism of amino acids, there are evidences of their effect in the increased insulin secretion by means of stimulation by these nutrients.

Conclusion

The interrelation between the metabolism of lipids, carbohydrates and proteins is regulated by PPAR. These receptors coordinate several metabolic pathways, by controlling the expression of proteins, such as LPL, acyl-CoA synthetase, FATP, acyl-CoA dehydrogenase, acyl-CoA oxidase and enoyl-CoA, which are involved in the adipogenesis and/or lipogenesis and lipolysis, in search of energy homeostasis, so as to propitiate the adaptation of the organism to different environmental stimuli, such as the increased intake of lipids and/or carbohydrates in medium and long term.

In the attempt to avoid glucotoxicity and lipotoxicity, which typically lead to obesity and diabetes, the expressions of PPAR α and isoforms are differentially increased in the tissues. The final result of their actions are: 1- In the liver: increased lipid oxidation and reduced hepatic insulin resistance, by the activation of PPAR α ; 2- In the adipose tissue: differentiation and increased size of adipocytes and lipogenesis by the activation of PPAR γ and, 3- In the muscle: increased lipid oxidation and glucose capture stimulated by the activation of PPAR α . Such effects increase sensitivity to insulin, whose synthesis and secretion can also be stimulated by this type of nuclear receptor when activated by their natural or synthetic ligands in pancreatic β cells.

Great part of the understanding of the mechanisms involved in the PPAR activation is based on studies which use synthetic agonists of these receptors in obese and/or type 2 diabetic patients. Although not many works assess the effects of different diet compositions on the activation of these molecules and their relation with hormones mainly produced by the adipose tissue such as leptin, there are evidences of the influence of macronutrients (lipids and carbohydrates), as well as the quantities ingested, on the PPAR activation, leading to increased lipolysis (PPAR α) or lipogenesis (PPAR γ). Besides, the effects of natural or synthetic ligands on the PPAR activation not only control the lipid metabolism, but strongly affect the mobilization of body amino acids and their degradation by the liver. It is also suggested that the PPAR activation can suppress the degradation of amino acids in the Islets of Langerhans and thus, contribute for the increased insulin secretion stimulated by amino acids in animal models.

Therefore, it is extremely important to elucidate the influence of dietary composition on these receptors, so as to allow the development of interventions aiming at preventing obesity and DM2 or assisting in the treatment of these diseases.

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