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FAMILY OF NUCLEAR PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS (PPARs): BIOLOGICAL ROLE IN METABOLIC ADAPTATION
PART III. PPARγ IN ENERGY HOMEOSTASIS AND FORMATION OF METABOLIC SYNDROME, HEPATOSTEATOSIS, CARDIOVASCULAR CONDITIONS AND FIBROSIS (report 1)

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ABSTRACT. Objective*. Analysis and summary of the current concept of biological role of nuclear peroxisome proliferator-activated receptor gamma (PPARγ) in the body, that is a transcription factor, simulating the expression of target genes that regulate different chains of adipogenesis, thermogenesis, energy homeostasis, providing balance of glucose and sensitivity of cells to insulin, secretion of adipokines, antiinflammatory, and antifibrotic effects.*

Materials and Methods. *Analytical review of scientific publications was performed using abstract databases of scientific libraries and text database of methodological and biological publications PubMed.*

Results*. Biological and physiological role of PPARγ in the body has been established. Its important role in the maintenance of energy homeostasis, hormonal secretion of fatty tissue has been found, as well as anti-proliferative, antioxidative, and anti-fibrotic effects upon its activation have been noticed. It was noted that PPARγ polymorphism or its dysfunction under the exposure to pesticides and other xenobiotics contributes to the formation of metabolic syndrome, type 2 diabetes mellitus, hepatosteatosis, obesity, chronic inflammation, and fibrosis.*

Key words: *Nuclear peroxisome proliferator-activated receptor gamma (PPARγ), ligands, adipokines, energy homeostasis, hepatosteatosis, type 2 diabetes mellitus, obesity, fibrosis.*

Family of nuclear receptors (NR) peroxisome proliferator-activated receptors (PPARs) belongs to the transcription factors of gene expression involved in metabolism of fatty acids, adipogenesis and sensitivity to insulin, regulating energy homeostasis in human and animals. It is presented by three subtypes — PPARα (NR_1C_1), PPARβ, synonym — delta (NR_1C_2) and PPARγ (NR_1C_3). These NR are expressed almost in all body cells, however, they differ in predominant tissue distribution, functions, and specificity of ligands (endogeneous or exogeneous links, connecting with NR and activating them). About 20 years ago, PPARα was found in the rodents that activates proliferation of peroxisome — subcellular organelles upon the exposure to a range of industrial compounds, in this regards, all three subtypes of PPAR were named somewhat out of date, however, they almost do not induce peroxisome proliferation in human [1, 2].

In this article we fixed on generalisation of data on the structure and functional peculiarities of PPARγ, since we provided the description of biological role of PPARα and PPARβ/δ in the previous issues of this journal*.

Three-dimensional structure of all three PPARs subtypes consists of ligand-binding domain (LBD) at C-terminal and DNA-binding domain (DBD) at N-terminal. After interaction with agonists (ligands), PPARs undergo translocation into the nucleus and heterodimerization with other receptors — nuclear retinoid acid receptor (RXR). PPARs function is modified by the range of co-activators and co-repressors, presence of which may

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either stimulate or inhibit receptor function, respectively. After binding to ligand, complex PPARs-RXR releases from co-repressor and binds to co-activator contributing to gene expression in DNA promotor zone (PPREs).

Three PPARs isoforms differ one from another by distribution in tissues, by ligand specificity and physiological role in the body, participate in lipid homeostasis and glucose level regulation (energy homeostasis). For example, PPARα are expressed at a high level in the metabolically active tissues, such as liver, heart, skeletal muscles, intestinal mucosa, and brown adipose tissue. This receptor participates in fatty acids metabolism, its activation reduces the level of lipids, and depression is accompanied by the development of obesity [1, 4, 5].

PPARβ/δ are presented throughout virtually all tissues. However, it prevails in the liver, intestine, abdominal fatty tissues, skeletal muscles where it participates in lipid metabolism. This receptor actively participates in β-oxidation of fatty acids, principally in the skeletal muscles and myocardium, and also regulates blood cholesterol and glucose level [1, 4, 6].

In its turn, PPARγ is predominantly expressed in the white and brown adipose tissue, and to a lesser extent, in the intestine, kidneys, reproductive and immune system (bone marrow, lymphocytes, monocytes, and macrophages), and in small amount — in muscles and nervous cells [1, 2, 3, 4].

Endogeneous and exogeneous PPARγ ligands. A wide spectrum of mono- and polyunsaturated fatty acids is presented as the endogeneous PPARγ ligands. Ligands with moderate affinity to PPARγ include metabolites of arachidonic, linolic, and linolenic acids. Essential eicosanoids, such as 8-(S)-hydroxyeicosatetraenoic acid (8-HETE), 15-desoxy-D12 and 14-prostaglandin J215d-PGJ2, are identified as the endogeneous PPARγ ligands. It is notable that 5-hydroxytryptamine (5HT), known as serotonin, is the agonist with the high affinity to PPARγ, however, physiological value of this fact has not been studied yet [8]. Natural PPARγ ligands include fats and oils, as well as isoflavons, flavonoids, including hesperidin, quercetin, etc. [11, 12]. It should be noted that natural fats, oils, isoflavons, and flavonoids are partial PPARγ activators, whereas such synthetic drugs as thiazolidinediones are complete agonists of this receptor, and they are applied as antidiabetic drugs [8, 11, 12].

Thiazolidinediones reducing insulin resistance in patients with type 2 diabetes mellitus occurred in late 1990. The first drug of this group — troglitazone occurred in 1997, however, due to its toxicity it was withdrawn from the market in 2000. It was shown that troglitazone activates PPARγ, increases cellular sensitivity to insulin, reduces glucose tolerance, inhibits progression of early atherosclerotic lesions [75]. Other drugs of this group — rosiglitazone and pioglitazone are limitedly used in the clinical practice as drugs till present time, although their application is accompanied with the range of side effects: increased risk of myocardial infarction, heart and hepatic failure. Compared with rosiglitazone, pioglitazone shows normalising effect on lipid profile reducing the risk of myocardial infarction, stroke, or heart failure. However, its clinical application is also limited due to the development of the range of side effects, including body weight gain with obesity, fluid retention in the body, and the risk of bladder cancer [75]. Despite of this, modern antidiabetic drugs — PPARγ activators — remain the golden standard of agents for management of type 2 diabetes and obesity. Some non-steroidal anti-inflammatory drugs, such as indometacin, fenoprofen and ibuprofen also may activate PPARγ, however, their affinity is poorer.

PPARγ overexpression in non-fatty cells is sufficient enough to stimulate their transformation into adipocytes. Furthermore, an increased level of circulating fatty acids in the body increases PPARγ activity leading to the increase of adipose tissue mass and development of obesity. At the same time, PPARγ-induced fatty activation increases sensitivity of tissues to insulin and to some extent prevents the development of diabetes mellitus. Both endogeneous and exogeneous agonists of PPARγ not only provide regulation of lipid and carbohydrate metabolism, but also have a potential to reduce intensity of inflammation, affect balance and function of immune cells, inhibit oxidative stress, improves endothelial function, participate in the functioning of reproductive system in cellular and molecular mechanisms of prevention of neurodegenerative processes, fibrosis, and formation of cancer [75, 76].

PPARγ in adipogenesis, accumulation, and metabolism of lipids. In the human body, PPARγ is the main regulator for adipocytes

differentiation, plays an important role in storage, metabolism of lipids and glucose homeostasis, and also stimulates metabolism and inflammation in the immune cells and proliferation of immune control cells [1, 2, 3, 4, 5]. PPARγ plays a central role in the regulation of expression of several hundreds of genes, providing systemic control of adipogenesis: differentiation of adipocytes, synthesis of adipocytokines (hormones secreted by fatty tissue), formation and transportation of lipoproteins, ketogenesis, glucose homeostasis, metabolism of the range of fatty acids, storage of fat in the body. PPARγ is expressed in adipocytes about 200-fold more compared with other cells. PPARγ activates almost all required genes for the process of differentiation of adipocytes from pre-adipocytes. First of all, these are genes regulating synthesis of AP2 protein, required for transfer of free fatty acids (FFA); perilipin 1 (PLIN1) covering the surface of mature lipid drops in adipocytes; uncoupling protein 1 (UCP1) — the main factor stipulating differentiation of adipocytes of brown adipose tissue (BAT), participating in adaptive thermogenesis. This protein also acts as uncoupler of mitochondrial oxidative phosphorylation, its synthesis and activity increase under the influence of the range of ecotoxicants, pesticides in particular. PPARγ also regulates gene expression providing synthesis of hormones — adipocytokines, adiponectin (ADPN) in particular [1, 2, 3, 4]. Furthermore, PPARγ regulates gene expression in lipogenesis providing synthesis of acetyl-CoA-arboxylase1 (ACC1) and acetyl-CoAcarboxylase-α (ACACA) — enzymes limiting the rate of fatty acids synthesis. PPARγ also regulates factor ELOVL4 that provides synthesis of very-long-chain saturated fatty acids and synthesis of long-chain polyunsaturated fatty acids which are unique for eye retina, sperm, and the brain [3, 4]. PPARγ also provides gene expression that control synthesis of malic enzyme 1 (ME1) using which acetyl-CoA is transported from mitochondria as a citrate, transforms cytosolic malate into pyruvate, as well as regulates synthesis of enzymes stearyl-CoAdesaturase-1 and delta-9-desaturase participating in fatty acids metabolism [2, 3, 4, 18].

PPARγ provides homeostasis of glucose in the body, regulating gene expression that control synthesis of catalytic glucose-6-phosphatase (G6PC), cytosolic glycerol-3-phosphate dehydrogenase-1 (GPD1), glucokinase (GCK), phosphoenolpyruvate carboxylase (PEPCK), pyruvate dehydrogenase-kinase-4 (PDK4), and other enzymes participating in carbohydrate metabolism [1, 2, 3, 15]. PPARγ also activates gene expression activating synthesis of the range of glucose transporters: GLUT4 and C-CBL-associated protein CAP (Fig. 1).

Furthermore, PPARγ regulates the range of mechanisms providing normal insulin secretion and tissue sensitivity to it, predominantly due to the synthesis of the range of hormones by the fatty tissue controlled by this receptor.

Gene PPARγ has separate promotor regions and 7 exons. This leads to the synthesis of 7 subtypes of mRNA: PPARγ1, PPARγ2, PPARγ3, PPARγ4, PARγ5, PPAR-6, and PPAR-7. Proteins obtained from PPARγ1 and PPARγ3 mRNA are identical, while PPARγ2 contains additional NH2–terminal region of 30 amino acids. All PPARγ isoforms play an important role in differentiation of adipocytes and differ in tissue distribution. For example, PPARγ1 is characterised by a wide range of expression in white and brown adipose tissue, cardiac muscle, large intestine and haemopoietic tissues, and to a lesser extent — in the liver, kidneys, and muscles. PPARγ2 is expressed exclusively in the fatty tissue, and it is more potent transcription activator [4, 7, 9]. Both PPARγ forms have an important value for differentiation of adipocytes, development of adipose tissue and provision of control over cellular sensitivity to insulin and glucose content in the body [1, 2, 4, 7]. However, PPARγ2 predominantly regulates formation of obesity as a response to an increased consumption of nutrients, and blockade of PPARγ2 in a genetically gross mice more intensely reduces accumulation of fat in adipocytes compared with normal mice [7, 24]. PPARγ1 predominantly activates genes regulating adipogenesis and accumulation of white fatty tissue while PPARγ2 predominantly provides the control over brown adipose tissue development. PPARγ3 is expressed in white and brown adipose tissue, intestine, and macrophages. PPARγ4, 5, 6 and 7 are predominantly expressed in macrophages and adipose tissue, actively participate in autophagy, inflammation and carcinogenesis along with the participation in glucose and lipid metabolism.

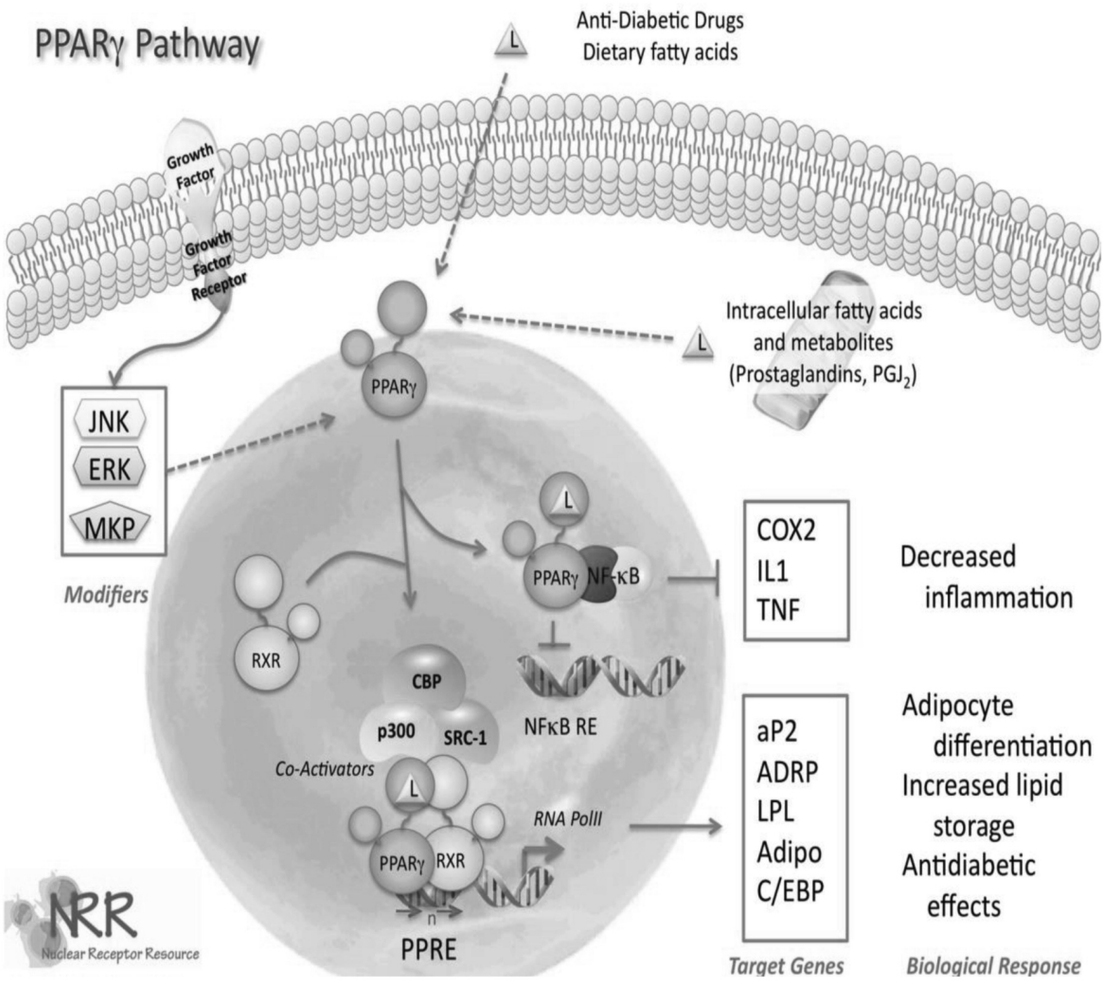

Fig. 1. PPARγ regulatory role involves differentiation of adipocytes, accumulation and metabolism of lipids, antidiabetics and anti-inflammatory effects [96].

In the recent years, brown and beige adipocytes, burning chemical energy of lipid oxidation for production of heat and provision of thermogenesis, attracts a great attention of investigators due to their ability to reduce intensity of metabolic disorders, accumulation of adipose tissue, and obesity. Brown adipocytes are developed in relatively homogeneous deposits of brown adipose tissue (BAT) while beige adipocytes develop in white adipose tissue (WAT) as a response to different stimuli upon the influence of cold and beta-adrenergic signals primarily. Brown and beige adipocytes are packed in cells with mitochondria that contain uncoupling protein 1 (UCP1) directing the flow of protons through mitochondrial membrane that leads to the increase in oxygen consumption and provides for the production of heat to protect from hypothermia. Mice that were genetically constructed with a high level of brown and beige fat show good withstand against body weigh gain in case of high-caloric diet and have healthy metabolic profile [33, 34]. And vice versa, animals with a reduced function of brown fat are more susceptible to obesity. In this regard, the search for pharmacological PPARγ antagonists that increase differentiation of brown and beige adipose cells providing energy for thermogenesis are currently high prospective in management of obesity [9, 10, 34, 44]. PPARγ is not only a main nuclear receptor that controls adipogenesis and storage of fat in adipocytes, but provides for the control of the start of new preadipocytes enrolment and differentiation into the mature adipocytes [17].

Physiological function of this nuclear receptor is very important for embriogenesis, and

rapid decrease of its activity or mutation leads to lipodystrophy and cachexia both in animals and human [13]. Heterozygous mutations in PPARγ genes of patients with family partial dystrophia were described [14]. Dominant negative PPARγ mutations were detected in insulin resistant subjects, and those who are suffering from diabetes mellitus, hepatosteatosis, hypertension, and obesity [15, 21, 22].

PPARγ and secretory function of adipocytes. One of the main PPARγ function is regulation of gene expression controlling secretion of the wide spectrum of biologically active substances or hormones, called adipokines, by adipose tissue, that actively participates in regulation of glucose and lipid homeostasis, as well as in reduction of inflammation and fibrosis [45, 46, 47]. Amount and nature of adipokine secreted by adipose tissue depends on ligand that stimulates PPARγ, amount of adipocytes containing in adipose tissue, and their size [48, 49]. PPARγ is not only a key factor controlling adipogenesis and adipose tissue mass, but also provides for the regulation of metabolic genes in these tissues, predominantly due to adipokine synthesis activation (Fig. 2).

Adipokines are produced in association with endogeneous ligands or exogeneous agonists (different natural products of animal or plant origin, medicinal products or xenobiotics, including pesticides) [48, 49]. PPARγ activation regulates synthesis of adipokines that is accompanied by increase in adipocytes, myocytes and hepatocytes sensitivity to insulin, stimulation of adipogenesis, increased consumption of glucose and fatty acids in these and other tissues, depression of glycolysis in the liver and reduced level of blood fatty acids [48, 49, 50].

The first adipokine, found in 1994 as a hormone secreted by adipose tissue, was leptin. Leptin is the adipokine secreted exclusively by

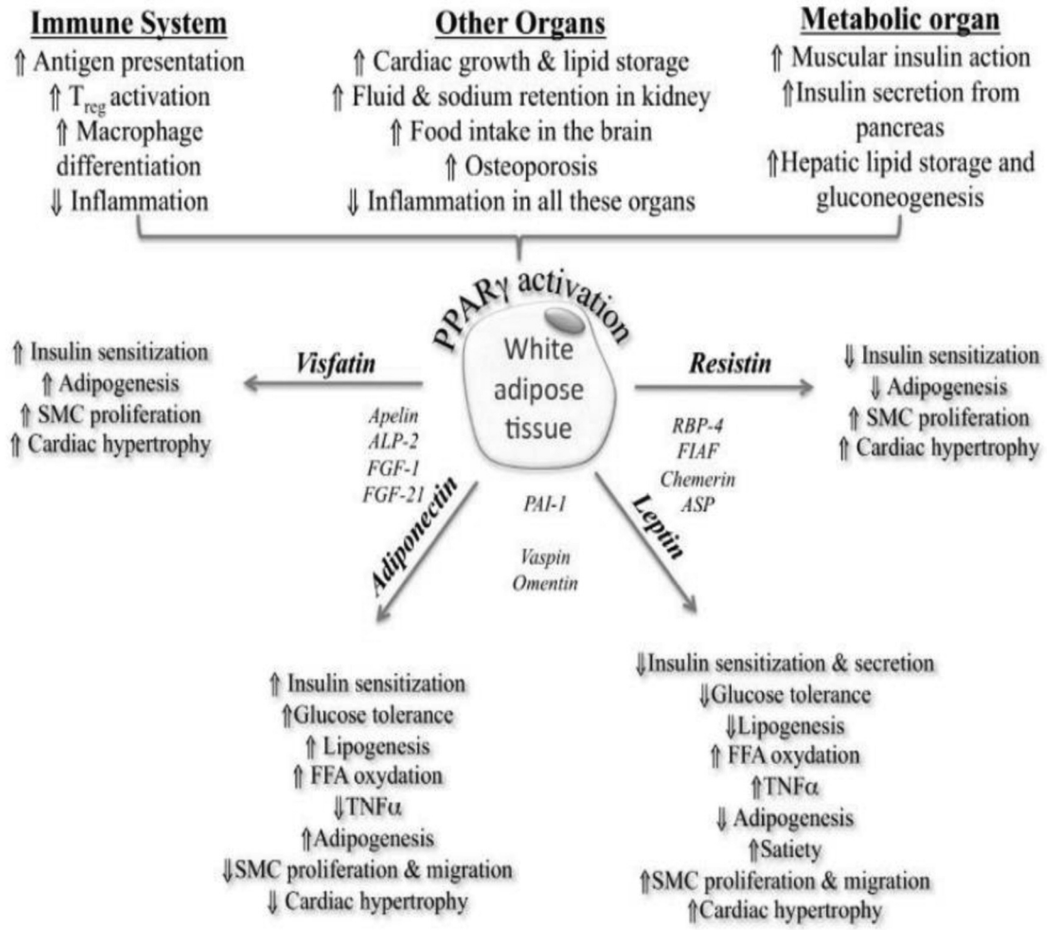

Fig. 2. PPARγ regulatory role of secretory function of adipocytes, producing hormones — adipokines that control homeostasis of lipids and glucose, inflammation, fibrosis, and other processes [48].

mature adipocytes, and its level in the blood positively correlates with the volume of body fatty mass [49]. The main functions of leptin include limitation of increasing the volume of adipose tissue due to the inhibition of PPARγ activity and provision of glucose homeostasis [48, 50]. Adipokine leptin plays a central role in glucose homeostasis controlling a range of different mechanisms (Fig. 2): 1) affect the sympathetic nervous system regulating a sense of satiation following meals and reduction of appetite [50, 51, 52]; 2) inhibits insulin secretion by pancreatic beta-cells [53, 54]; 3) reduces sensitivity of receptors of peripheral cells to insulin limiting consumption of glucose and lipids [55, 56]; increases synthesis of tumour necrosis factor-α (TNF-α) for limitation of increase of the volume of adipose tissue and inhibition of adipogenesis [57, 58], and also contributes to the formation of insulin resistance. There is an assumption that TNF-α, genes of which control PPARγ, is one of the key metabolism regulators.

Long-term consumption of energy food is accompanied by PPARγ hyperactivation with compensatory increase in leptin synthesis with the development of leptin resistance that may be accompanied by the development of systemic insulin resistance, metabolic syndrome, diabetes, fatty hepatosis, and obesity [58, 59].

Opposite role is played by another hormone, secreted by adipose tissue — adiponectin. Contrary to leptin, it increases sensitivity of tissue receptors to insulin via activation of the range of protein kinases, forms glucose tolerance, accelerates differentiation of adipocytes and fatty acid oxidation, reduces content of lipids in muscles and liver due to activation of AMP-activated protein kinases [61, 62, 63]. If leptin activates synthesis of tumour necrosis factor α (TNF-α) that contributes to the reduction of insulin secretion and sensitivity of cellular receptors to it forming insulin resistance [59], then adiponectin, in its turn, rapidly inhibits synthesis of this cytokine contributing to the increased insulin secretion, reduced insulin resistance and prevents development of obesity [Fig. 3]. Inhibition of adiponectin synthesis upon the exposure to a range of xenobiotics, including pesticides, increases the risk for the development of insulin resistant diabetes, steatohepatosis, and obesity [48, 59, 61]. Adiponectin not only contributes to the development of glucose tolerance, but also stimulates its disposal via activation of protein kinase [60]. Counterbalance of leptin and adiponectin in the human body has been insufficiently studied, some controversial facts were noted: on the one hand, leptin inhibits appetite, on the other — under developed leptin resistance, it contributes to obesity, however, their main functions along with adiponectin are contrary. While leptin reduces glucose tolerance, stimulates its synthesis, adiponectin controls its blood level, increases sensitivity of cellular receptors to insulin [62, 63], (Fig. 2). Upon the increase of blood glucose level, PPARγ activates synthesis of adiponectin which inhibits expression of micro-RNA (m-RNA), encoding hepatic glucose-6-phosphatase (G6PC) and PEPCK that participate in glucose synthesis, thus inhibiting its production [62]. Furthermore, adiponectin stimulates expression of glucose transporters that increases its disposal and also inhibits synthesis of glycogen in muscles [48, 62].

In recent years, a new hormone, resistin, was found that is secreted by adipocytes of visceral fat, skeletal muscles and by macrophages, and the same as leptin, it is associated with a formation of insulin resistant diabetes and obesity [48, 64, 65, 66]. It also reduces cellular sensitivity to insulin, inhibits adipogenesis, increases accumulation of lipids in tissues, and its increased synthesis is associated with the development of insulin resistance, metabolic syndrome and steatohepatosis [65, 66], (Fig. 2).

Additionally, it was established that PPARγ controls synthesis of such adipokines as vaspin and insulin-like hormones — visfatin and apelin in adipose tissue which increase insulin secretion and cellular sensitivity to insulin and reduce progression of insulin resistant diabetes and obesity in the same way as adiponectin [67, 68, 69].

Therefore, adipose tissue hormones under PPARγ control play a key role in lipid metabolism and glucose homeostasis, but at the same time show differentially directed action. If adiponectin, visfatin, vaspin, and apelin under the action of PPARγ increase tissue sensitivity to insulin and glucose tolerance, activate adipogenesis and lipogenesis, then leptin and resistin reduce insulin secretion and cellular sensitivity to it, inhibit adipogenesis and lipogenesis. Furthermore, leptin causes a sense of satiation — reduces appetite. In the majority of

its functions, adiponectin acts unidirectionally with hormones of visfatin group, but while adiponectin reduces proliferation and migration of smooth muscle cells (SMC) and myocardial hypertrophy, visfatin, vaspin, apelin and leptin as well as resistin activate proliferation and migration of SMC and contribute to the development of proliferative processes, fibrosis and myocardial hypertrophy. Interaction of adipose tissue hormones in energy homeostasis and development of metabolic disorders requires further exploration.

Adiponectin and visfatin group hormones provide for the control of metabolic homeostasis and induce inhibition of diabetogenic factors. Inhibition of synthesis of these adipokines under the influence of exogeneous factors, including pesticides, contributes to the formation of steatohepatosis, insulin resistant syndrome, metabolic syndrome, and obesity.

PPARγ and metabolic syndrome. It was proved that metabolic syndrome is a consequence of not only an energy diet and hypodynamia, but also a congenital or acquired PPARγ dysfunction, as well as dominant negative mutations in this receptor [16, 24]. Currently, metabolic syndrome is one of the main epidemics in the world associated with obesity, insulin resistance, type 2 diabetes, and cardiovascular conditions, that is the main cause of disability and mortality. Currently, metabolic syndrome is established in a quarter of world adult population [15, 18, 21, 22, 25]. Its prevalence further increases among adults and children, predominantly due to a life style that is characterised by energy food in combination with a low physical activity [18, 19]. Long-term consumption of energy food with an excessive amount of fats is accompanied by permanent dysfunction of PPARα, PPARβ and PPARγ resulting in the development of impaired processes of fatty acids oxidation and lipid accumulation in hepatic adipose cells, muscles, and other organs. These processes are more intense in people with PPARγ gene mutations, as well as its co-expressors, and in particular, co-activators or RXR [35, 36, 37, 38, 39, 40, 41, 42, 43]. Furthermore, intensification of these processes may occur upon activation of PPARγ function following exposure to different xenobiotics, including pesticides [20, 21, 22, 25, 39, 41].

Metabolic syndrome is a clinical complex of syndromes determined by the imbalance of energy homeostasis associated with impaired storage and utilisation of energy. It is characterised by abdominal obesity, hypertension, dyslipidemia with an increased level of blood triglycerides, cholesterol and low-density lipoproteins with a reduced level of high-density lipoproteins, as well as insulin resistance with an increased fasting blood glucose level and formation of prothrombotic and proinflammatory compounds [27, 28, 34, 39]. Subjects with metabolic syndrome have a high risk of type 2 diabetes mellitus and cardiovascular conditions [29, 30, 31, 32, 40, 41, 42, 43]. It has been recently proved that metabolic syndrome associated with PPARs dysfunction and obesity induces under active inflammation in different tissues and increased sensitivity to other abnormal conditions, such as hepatosteatosis, sleep disorders, gallstone disease, polycystic ovarian syndrome, asthma, and some types of cancer [21, 23, 28, 31, 40, 41, 42, 43].

PPARα is widely presented in the liver, and it is closely associated with gene transcription related to fatty acids oxidation. PPARα activation leads to the body weight loss and reduction of steatohepatosis and metabolic syndrome intensity, while the reduction of its function leads to steatohepatosis and obesity. Contrary to it, PPARγ in healthy subjects is presented in the liver in a very low amount (9–12 % of expression in adipose tissue). At the same time, patients with metabolic syndrome and non-alcoholic fatty liver disease show abnormally high PPARγ expression in the liver. Increase of PPARγ expression is a sign of hepatic steatosis and some authors attribute to it a causative role in the development of steatohepatosis via activation of mechanisms that initiate lipogenic genes and genes of adipogenesis [81, 82]. In PPARγ-null mice, there is a complete lack of adipose tissue suggesting its a key role in differentiation of adipocytes, lipogenesis and lipid accumulation in adipose tissue. In case of metabolic syndrome and steatohepatosis, increased expression of PPARγ in the liver takes place along with a reduced PPARα activity. An energy diet contributes to activation of synthesis and oxidation of fatty acids that is accompanied by generation of free radicals, formation of oxidative stress in endoplasmic reticulum of hepatocytes with the antioxidative potential reduction: depletion of glutathione (GSH) and inhibition of superoxide dismutase (SOD) activity

with the reduction of systemic antioxidative plasma ability. There is a concomitant formation of insulin resistance and hypoadiponectinaemia — inhibition of adiponectin synthesis that normally reduces fatty accumulation and increases tissue sensitivity to insulin, as well as the increase of leptin secretion [81–85]. PPARγ activation along with an impaired PPARα regulation is accompanied by high expression of lipogenic SREBP-1c factor (sterol regulatory element binding protein-1c) with a depletion of progenitors of α-linolic acid - long-chain polyunsaturated fatty acids (n-3 LCPUFA) and accumulation of triacylglycerols and F_2-isoprostanes in hepatocytes, contributing to formation of steatohepatosis and obesity [83–85] (Fig. 3).

Role of PPARγ gene polymorphysm in the development of metabolic syndrome, steatohepatosis and obesity was determined. Dominant negative PPARγ mutations are the reason for many disease characterised by severe insulin resistance, development of type 2 diabetes, metabolic syndrome, steatohepatosis, obesity, and hypertension. PPARγ-Pro12Ala variant of polymorphism is permanently associated with the development of metabolic syndrome, insulin resistance, and obesity. Furthermore, patients with 12Ala allele had a higher risk for severe steatohepatosis and hepatic fibrosis. Pro12Ala polymorphism is associated with a high TG level in the blood serum, alkaline phosphatase, and excessive body weight, whereas C161T polymorphism is associated with the increase of triglycerides and total cholesterol [84, 85].

Therefore, PPARs family, especially inhibition of PPARα and β function and activation of PPARγ plays a key role in the formation of steatohepatosis, metabolic syndrome and obesity, especially under the exposure to xenobiotics — obesogens. In this regard, in recent years this family of nuclear receptors attracts a great attention as a therapeutic target for management of metabolic syndrome, steatohepatosis, non-alcoholic fatty liver disease, and obesity [84, 85]. Considering that PPARα contributes to the increase of mitochondrial beta-oxidation of fatty acids and to the reduction of fat accumulation, successful attempts were taken to apply PPARα agonists (fenofibrates, telmisartan, cod liver oil, seal oil, etc.) for management of metabolic syndrome, steatohepatosis and obesity both under experimental and clinical settings [85, 86, 87]. PPAR β agonists — besafibrates, GW 501516 also

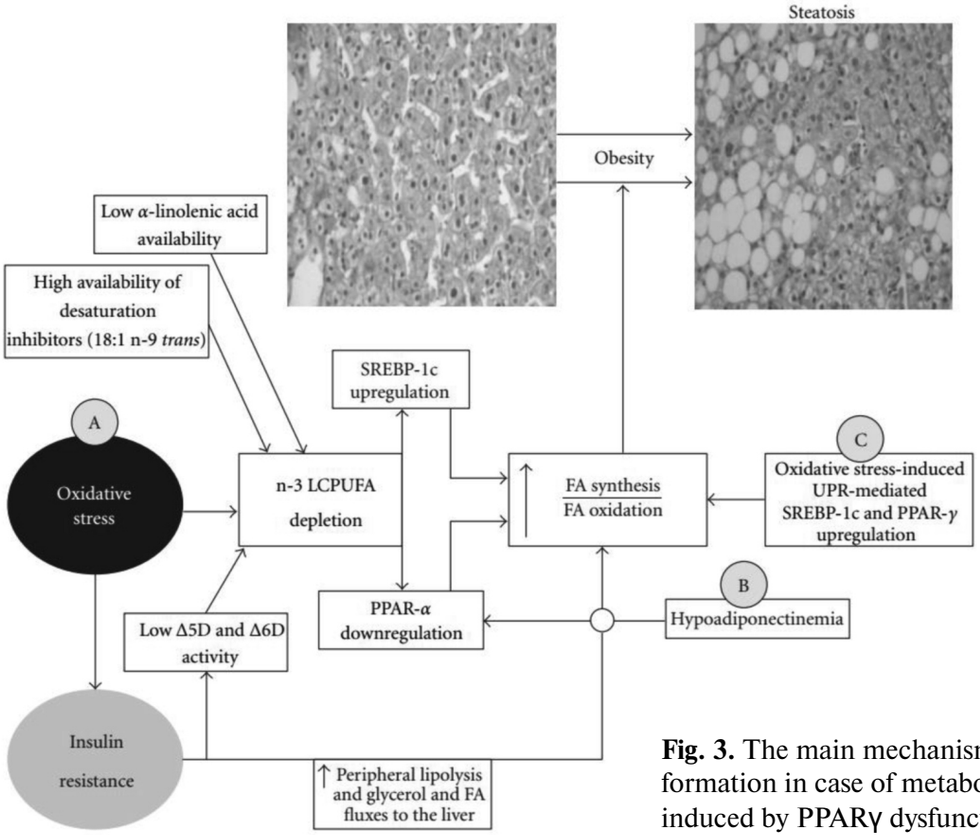

Fig. 3. The main mechanisms of obesity formation in case of metabolic syndrome induced by PPARγ dysfunction [84].

inhibit the development of fatty liver disease in the experiment, however, effective PPARβ agonist for management of steatohepatosis in human has not been proposed yet [85]. In recent years, successful application of PPARγ inhibitors in the experiment, resulting in inhibition of adipogenesis and fat accumulation (rapamycin and timcodar), were reported [88].

PPARγ and dysfunction of cardiovascular system. PPARγ is expressed in all cells of cardiovascular system (CVS): in cardiomyocytes, smooth muscle cells, monocytes, macrophages, endothelial cells [48, 71]. In mice with blocked PPARγ, development of myocardial hypertrophy and heart failure is observed [71]. PPARγ cardioprotective effect includes formation of cardiomyocyte tolerance to glucose due to the activation of adiponectin and visfatin group hormones synthesis, provision of energy homeostasis and control over oxidation of fatty acids, as well as the reduction of sensitivity to free radicals which are excessively formed in case of diabetes and obesity [48, 71, 72]. Due to its important role in metabolism, PPARγ is considered as a potential mediator in case of vascular conditions [73]. PPARγ and adipokines controlled by it inhibit inflammatory process in the coronary vessels and cardiac muscle, optimize endothelial function [48, 74, 75]. This receptor and adipokines not only inhibit the transcription activity of pro-inflammatory factors (TNF-α, NF-kB, pro-inflammatory cytokines, etc.), but also reduce the induction of molecules that form systemic hypertension [76]. For example, adiponectin and pelin reduce secretion of proinflammatory cytokines, increase cellular sensitivity to insulin and optimize energy homeostasis. In its turn, activation of leptin secretion upon the exposure to endogeneous and exogeneous agonists is accompanied by hyperreactivity of sympathetic nervous system, formation of diabetic cardiomyopathy with left ventricular hypertrophy, with further cardiac fibrosis with diastolic and systolic dysfunction [48, 70–75, 84] (Fig. 4).

Therefore, considering cardioprotective PPARγ effects, it should become an active target for therapeutic agents used for management of cardiovascular conditions.

PPARγ and its role in formation and progression of fibrosis. Fibrosis is an important characteristic of many chronic diseases. Its development contributes to the reduced function of different organs. For example, majority of cardiac diseases (CAD, myocardial infarction, hypertension, bacterial endocarditis, etc.) are accompanied by the development of focal or diffuse cardiac fibrosis that lead to the development of chronic heart failure. Hepatosteatosis, hepatic cirrhosis, chronic hepatitis due to the development of hepatic fibrosis are accompanied by the reduced detoxification and synthetic liver function. Outcome of many pulmonary disease is focal or diffuse pneumosclerosis with the development of respiratory fail-

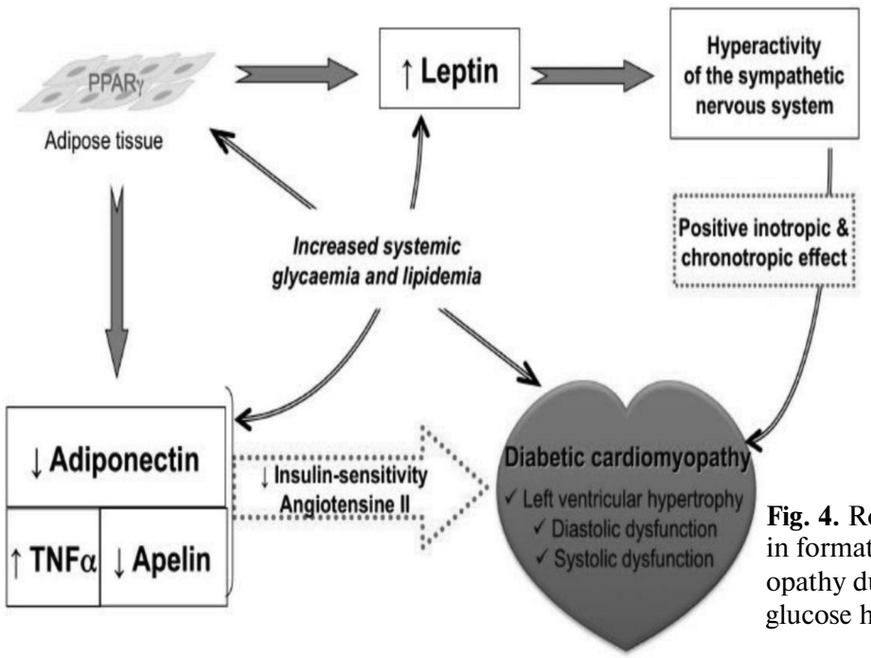

Fig. 4. Role of PPARγ dysfunction in formation of diabetic cardiomyopathy due to impaired lipid and glucose homeostasis [48].

ure. In case of systemic scleroderma, there is a progressive fibrosis affecting condition and function of the range of organs (skin, kidneys, liver, lungs, etc.). Many diseases of the liver, kidneys, skin, brain, endocrine and reproductive system are also accompanied by the development of sclerotic processes with a reduced function. Despite the wide prevalence of fibrosis and its important role in the reduced function of different organs and systems, molecular and regulatory mechanisms of its formation have not been sufficiently studied. Unfortunately, as a result there are no efficient therapeutic agents able to stop or slow down the progression of fibrosis till now, since mechanisms of its formation and progression have not been sufficiently studied yet.

In recent years, it was established that PPARγ plays an important antifibrotic role not only in the formation of fibrosis, but also in the inhibition of its progression in different organs [82–84, 89]. It was detected that in organs with developing fibrosis, PPARγ is presented at a low level and therefore, it is still unclear whether fibrosis is a reason for the reduction of its expression and activity in this organ or congenital or acquired PPARγ hypofunction and its signal pathways contributed to the formation and progression of fibrosis, including, for example, keloid scars in case of burn disease. Basis for the formation of fibrosis includes excessive deposition of collagen and other components in the extracellular matrix (ECM) upon inappropriate restorative function of connective tissue that is accompanied by the matrix remodelling, fibrogeneis and impaired tissue homeostasis [82–84]. The main effector cells in the development of fibrosis are overactivated fibroblasts as the response to overexpression of transforming growth factor TGF-β with participation of kinases [82, 83]. As the response to TGF-β expression, fibroblasts show synthesis of the high levels of L-smooth muscle actin (α-SMA), contributing to the transformation of progenitor cells into myofibroblasts, characterised by the increased synthesis of proteins of the extracellular matrix resistant to apoptosis [106]. This process of differentiation into fibroblasts is called epithelial-mesenchymal transition for which TGF-β is considered as a key regulator [82–84]. TGF-β in cooperation with the range of cytokines (IL-4, IL-6, IL-8 and IL-13), connective tissue growth (CTG) factors and platelet-derived growth factor (PDGF) form fibrosis, and, therefore, they are an innovatory target of antifibrotic therapy. PPARγ inhibits TGF-β-mediated pathway of fibrosis formation, and reduction of PPARγ function contributes to the formation of fibrosis in the skin, lungs, liver, heart, kidneys, pancreatic gland and other organs [82–84, 89]. The range of endogeneous factors, cytokines and ligands inhibit PPARγ function and contribute to the progression of fibrosis: TGF-β, CTG, PDGF, Wnt, leptin, N-cadherin, fibronectin, lysophosphatidic acid (LPA), as well as free radicals and hypoxia [82–84]. In its turn, PPARγ-regulated adiponectin inhibits fibrogenesis.

Special interest of investigators is attracted to the exploration of mechanisms for the formation of cardiac fibrosis leading to the development of chronic heart failure and disability. Cardiofibrosis is characterised by the abnormal accumulation of extracellular matrix in myocardial interstitium (ECM). ECM consists of collagens, elastic fibres, glucosaminoglycans and glycoproteins — products of fibroblasts [76]. Under physiological conditions, ECM is required for the maintenance of normal structure and function of the heart. Its formation and degradation are in dynamic balance. In case of abnormal conditions due to PPARγ function inhibition, excessive activation of renin-angiotensin-aldosterone system (RAAS), inhibition of metalloproteinases synthesis, excessive secretion of some regulatory cytokines, such as transforming growth factor beta (TGF-beta), pro-inflammatory cytokines: TNF-α, IL-6, IL-1, IL-15 and other, as well as increased secretion of such hormones secreted by the adipose tissue as leptin, resistin and visfatin group hormones, dynamic balance become impaired, ECM becomes impacted with a final formation of cardiac fibrosis [76]. This abnormal process is a beginning for cardiac remodelling and it directly leads to the impairment of cardiac function, arrhythmia or heart failure. Increased secretion of pro-inflammatory cytokines, leptin, resistin and visfatin group hormones activate tissue inhibitor of metalloproteinase-1 (TIMP-1), increased expression of metalloproteinases, nuclear factor (NF-kB), activation in the DNA promotor zone of peroxisome proliferator response elements (PPRE), regulating increased gene expression, activating synthesis of collagen, pro-inflammatory and pro-oxida-

tive factors that form inflammation, oxidative stress in ECM accompanied by impaired endothelial function, formation of cardiac hypertrophy and cardiac fibrosis [76, 77, 78, 80, 83].

PPARγ agonists inhibit the effect of nuclear factor NF-kB, PPRE, gen expression activating synthesis of pro-inflammatory and pro-oxidative factors, inhibit synthesis of fibronectin, expression of type I collagen, increase apoptosis of fibroblasts, secretion of adiponectin in adipocytes that contributes to the reduced proliferation and migration of fibroblasts, smooth muscle cells, prevents development of cardiac hypertrophy, as well as fibrosis progression [76–80] (Fig. 5).

A large preventive role of histone deacetylase (HDAC) in the reduction of myocardial function and cardiac remodelling, activity of which is increased by PPARγ agonists [78, 80]. PPARγ activation prevents or slows down the formation of cardiac fibrosis, regulating metabolism, reducing severity of metabolic disorders [77], synthesis of pro-inflammatory cytokines and pro-oxidative factors that maintain balance of immune cells by inhibition of oxidative stress and improvement of endothelial function [75–79], therefore, PPARγ is a prospective target for management of cardiovascular diseases [79]. At the same time, PPARγ 1–7 have different biological functions in different types of cells and play the important role in the prevention of cardiovascular diseases, including hypertension, atherosclerosis, diabetic cardiomyopathy, angiogenesis, valve calcification, aortic aneurysm, CAD, and cardiac fibrosis [76–80]. Administration of PPARγ agonists — antidiabetic drugs (rosiglitazone) in combination with losartan, telmisartan or calcium blocker (felodipine) reduces severity of cardiac fibrosis due to the reduced deposition of type I–III collagen via inhibition of TGF-beta and other pro-inflammatory and pro-oxidative factors [76, 83]. Some natural products — PPARγ agonists also contribute to this [75].

Some molecules and medicinal products with antifibrotic potential have been studied, and they include: adiponectin, E-cadherin, eplerenones, statins, some angiotensin II inhibitors (irbesartan, telmisartan, etc.), especially in combination with PPARγ agonists — thiazolidinediones, (Fig. 6), where a regulatory role of ligand-PPARγ agonists, increasing its expression and decreasing the development of fibrosis in different tissues, is provided.

Undoubtedly, exploration of the mechanisms for fibrosis formation in different organs and development of the effective and safe PPARγ agonists for its management should be continued.

Therefore, PPARγ activation, its polymorphism or acquired mutations of receptor and its signal pathways under the exposure to pesti-

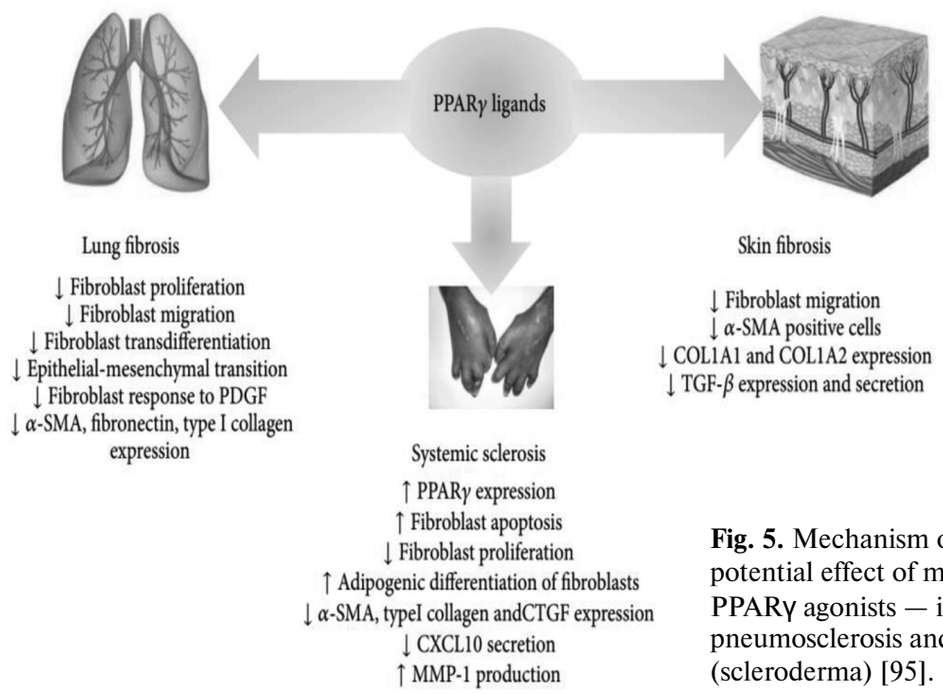

Fig. 5. Mechanism of formation of potential effect of medicinal products — PPARγ agonists — in management of pneumosclerosis and systemic sclerosis (scleroderma) [95].

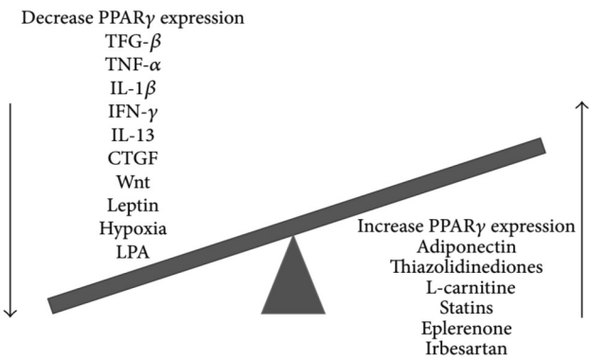

Fig. 6. Effect of different molecules on the reduction and increase of PPARγ expression [95].

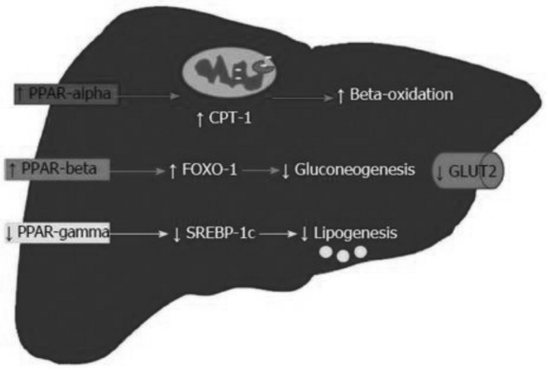

Fig. 7. A potential effect of medicinal products — PPARα and PPARβ activators and PPARγ inhibitors in management of non-alcoholic fatty liver disease [85].

cides or other xenobiotics are accompanied by activation of adipogenesis with a formation of new adipocytes, predominantly of white fat, activation of lipogenic factors (SREBP -1c, etc.) and synthesis of fatty acids and triglycerides with their accumulation in the liver and insulin resistance development. These processes are accompanied by the redox imbalance, formation of oxidative stress, mitochondrial dysfunction, activation of pro-inflammatory genes and synthesis of pro-inflammatory factors (NF-kB, AP-1, TNF-β, etc.), chemokines, cytokines, and hypoadiponectinaemia that contributes to the formation of steatohepatosis and its progression with a transition into non-alcoholic fatty liver disease (steatohepatitis). Development and progression of steatohepatosis is mediated by the reduction of PPARα and PPARβ function with a further reduction in fatty acids oxidation, with oxidation of long-chain polyunsaturated fatty acids (n-3, LCPNFA), predominance of synthesis of fatty acids over their oxidation. These processes are accompanied by the formation of metabolic syndrome, steatohepatosis, type 2 diabetes mellitus, and obesity, progression of chronic inflammatory processes in different organs with a transition to fibrosis. In recent years, successful attempts of steatohepatosis and obesity management using PPARα and PPARβ activators [85, 86, 87] and PPARγ inhibitors — rapamycin, timcodar [88], were made. The schedule of the potential effect of application of PPARα and PPARβactivators and PPARγ inhibitors are provided in Fig. 7.

Therefore, application of PPARα and PPARβ agonists, as well as PPARγ antagonists is the most prospective in management of steatohepatosis, metabolic syndrome, and obesity. Application of PPARγ, as well as PPARα and β as the target for management of metabolic disorders, steatohepatosis, obesity, and fibrosis appears to be the most prospective.

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