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FAMILY OF NUCLEAR PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS (PPARs): BIOLOGICAL ROLE IN METABOLIC ADAPTATION
PART III. PPARγ AND ITS ROLE IN AUTOPHAGY, INFLAMMATION, CARCINOGENESIS AND REPRODUCTIVE SYSTEM UPON THE EXPOSURE TO XENOBIOTICS (report 2)

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ABSTRACT. Objective*. Analysis and summary of the current concept of biological and physiological role of nuclear peroxisome proliferator-activated receptor gamma (PPARγ) in the development and functioning of reproductive system, in regulation of autophagy, inflammation, and carcinogenesis.*
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*. Physiological role of PPARγ in the development and functioning of reproductive system organs was established; its important role in energy supply for ovulation processes, oestrogen secretion, functioning of placenta, claustrophobia, embriogenesis was determined. Its regulating role in the processes of autophagy, inflammation and carcinogenesis was established. Pro-inflammatory, antioxidative, anti-proliferative effects, inhibition of tumour growth and metastasis of cancer cells upon PPARγ activation were found. Metabolic and endocrine disrupter effects of xenobiotics due to PPARγ dysfunction were noticed. Use of PPARγ as a therapeutic target upon management of reproductive disorders, inflammatory processes and cancer was justified.*
Key words: *Nuclear peroxisome proliferator-activated receptor gamma (PPARγ), reproductive system, autophagy, inflammation, carcinogenesis, synthetic agonists and antagonists.*

Identification of hormonal nuclear peroxisome proliferator-activated receptor gamma (PPARγ) and its endogeneous and exogeneous ligands-agonists, and exploration of its biological role in the body showed that it is a key regulator of energy homeostasis that provides for the differentiation of adipocytes, lipogenesis, fat accumulation, secretory function of adipocytes, as well as the reduction of glucose in blood serum and increase of insulin sensitivity in tissues. In recent years, it was established that PPARγ is presented in all organs and tissues of the body, and it implements psychotropic biological effects associated with regulation of autophagy, inflammation, fibrosis, and carcinogenesis. PPARγ regulates gene expression that control synthesis of pro-anti-inflammatory, antioxidative, and anti-fibrotic factors, modulates phylogenetic and self-renovating mechanisms of cells [1, 2, 3]. PPARγ plays a great role in the development and functioning of all structures of reproductive system.

PPARγ functions in a close cooperation with other isotopes of this receptor — PPARα and PPARβ. Coordinated functioning of all three PPARs isotopes provides energy homeostasis, redo balance, maintains physiological level of blood glucose and cellular sensitivity to insulin, prevents the development of metabolic disorders, type 2 diabetes mellitus, hepatosteatosis, obesity, inflammation, fibrosis, and carcinogenesis.

In its turn, a toxic effect of ecological chemical factors (pesticides and other xenobiotics, some medicinal products, stress, infectious agents) leads to dysfunction of PPAR α, β or γ that is accompanied by the development of different disruptor endocrine disorders. Many of these factors activate adipogenesis and lipogenesis, contribute to the development of metabolic disorders and obesity, and therefore, they are called obesogens. Exposure of other factors to

PPARα, β or γ contributes to the disorders of cellular differentiation and functioning of many organs and systems of the body (hepatitides, cardiovascular, endocrine, reproductive, etc.) that is accompanied by the formation of chronic inflammatory processes with a further development of fibrosis, tumour growth, development and progression of different diseases. Exploration of the role of PPARγ and other isotopes of this hormonal receptor in autophagy, inflammation, carcinogenesis, functioning of the reproductive system and mechanisms of formation of disruptor endocrine disorders upon the exposure to pesticides and other xenobiotics is of special interest.

PPARγ and its role in autophagy. In December 2016, among 273 pretenders for the Nobel Prize for Physiology and Medicine, it was awarded to the scientist Yoshinori Ohsumi for scientific justification of the mechanisms regulating autophagy. During the last 20 years it has been proved that a large amount of cellular content: products of lipid metabolism, large protein complexes, even entire damaged organelles, defects of mutation (micro nuclei, etc.), as well as bacteria and viruses are disposed in different cells by the special formation — automorphism [1–8]. Autolysophagosome is formed from confluence of vacuole sequestrated from endoplasmatic reticulum — automorphism with lysosome containing acidic hydrloases for digestion of the cellular content (Fig. 1).

As early as 1992, Y. Ohsumi identified and characterised 15 key genes involved in the process of autophagosomes formation. Transformation of the cellular content by small components in autolysophagosome provides cell with nutritive and building blocks (amino acids, nucleotides, fatty acids, glucose, etc.) for renewal of its further functioning as the mechanism of sanogenesis and control. In recent years, it has been proved that in a transcriptional coordination of autophagy, the key role is allocated to nuclear receptor PPARγ and farnesoid nuclear receptor (FXR) that regulate expression of more than 200 genes participating in regulation of autophagy and playing the main role in maintenance of energy homeostasis and metabolism, as well as in sanogenesis and self-renovation of cells [9, 10].

It has been shown that autophagy plays a certain role in physiological death of cells of the first type — apoptosis [11, 12], and also has an important value in embriogenesis, ageing, congenital and adaptive immunity, neurodegenerative diseases, diseases of the heart and skeleton, metabolic diseases, etc. [1–12]. Disorders in the mechanisms of autophagy are associated with the development of inflammation, fibrosis, accumulation of mutations in the cells, with formation of cancer and ageing [9–13].

Intracellular homeostasis requires constant balance between biosynthetic and catabolic processes. In general, eucariotic cells utilize two mechanisms of disposal and biosynthesis: proteasomes and autophagy, however, only autophagy is able to destruct whole organelles and elements of mutation. Three types of autophagy was described: macroautophagy (in autophagosomes), microautophagy (in

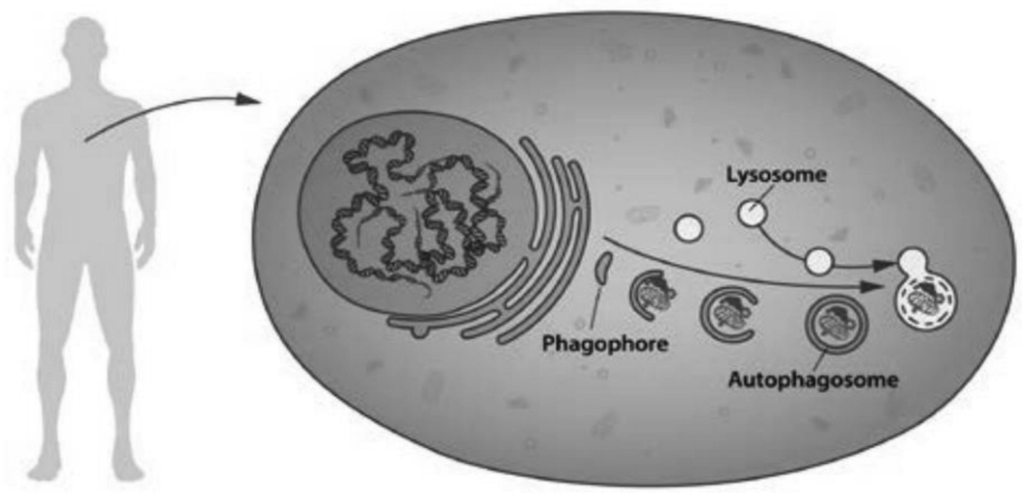

Fig. 1. Mechanism of formation of autophagosomes and phagolysosomes [1].

organelles — mitochondria, proteasomes, etc.), and chaperone-mediated autophagy [15, 20]. Autophagy takes place upon the basal levels in the majority of tissues and contributes to the routine circulation of cytoplasmic components. However, autophagy may be activated by changes in the environmental conditions such as starvation or exposure to physical and chemical factors, as well as infectious agents. Additionally to the circulation of cellular components, autophagy participates in the development, differentiation, and remodelling of tissues in different organisms [20]. Surprisingly, but autophagy may serve both for the protection of cells and provision of their vital activity and contribution to the cellular damage. Variants of possible role of autophagy in health and disease are provided in the table.

Studies of the range of authors showed that the intensity of autophagy correlates with certain diseases. Its inadequacy is associated with the development and progression of many conditions, including inflammation, cancer, neurodegenerative diseases (Parkinson disease, Huntington disease, Alzheimer disease, prion diseases, amyotrophic lateral sclerosis, etc.), as well as metabolic diseases, obesity, and even ageing [107, 108, 109]. Autophagy is a adaptive strategy which helps a cell to remove damaged blocks, organelles, infectious agents, and increases surveillance. About 300 genes were identified in regulation of autophagy, and their expression is performed by PPARα and PPARγ, as well as by farnesoid receptor (FXR) participating in metabolism of bile acids [12, 13, 14]. Dysfunction of this receptors reduces processes of autophagy and contributes to the development and progression of many abnormal processes, although mechanism of regulation of autophagy pathway by the nuclear receptors has not been completely studied. Studies of the processes of autophagy regulation will contribute to optimisation of the disease and ageing control, as well as health strengthening.

PPARγ and inflammation. Currently PPARγ is considered as an important modulator of inflammation and immunity in case of different abnormalities of inflammatory nature, including bacterial infections of the lungs and central nervous system, sepsis, granulomatosis, cancer, etc. [14, 16, 20, 21]. PPARγ is represented in all cells, participating in inflammation: white blood cells, macrophages, as well as in cells of T- and B-cell immunity. Due to the growth of antibiotic resistance, it is reasonable to study PPARγ ligands as the additional anti-inflammatory therapy.

A great role in the formation, as well as in inhibition of inflammatory processes in the body is played by hormones of adipose tissue which gene expression is controlled by PPARγ. Adipose tissue has an important role in human inflammatory diseases [25]. At the same time,

Table

Potential biological and physiological role of autophagy [20]

Abnormal process	Positive effects of autophagy	Negative effects of autophagy
Cancer	Cancer suppressor: activation of cellular death of 1st and 2nd type	May reduce efficiency of some anti-tumour agents, increase surveillance of cancer cells by elimination of damaged macromolecules or organelles
Liver diseases	Phagocytosis of non-functioning endoplasmatic reticulum and other organelles	Excessive autophagy impairs synthetic function of the liver
Myopathy	Activation of autophagy may compensate defects of lysosome function	Excessive autophagy may worsen the function of myocytes
Neurodegenerative diseases	Disposal of forming protein aggregates for the prevention of their toxic effects	Excessive autophagy may activate apoptosis of cells of the nervous tissue
Infectious diseases	Destruction of bacterial and viral agents in phagolysosomes	Activation of caspase-dependent apoptosis and attenuation of the immune response

adipose tissue, as an endocrine organ, regulates both pro-inflammatory and anti-inflammatory microenvironment depending on PPARγ function [26].

Adipose tissue is the place for formation of the range of pro-inflammatory cytokines — tumour necrosis factor α (TNF-α) and some interleukins [25, 25]. It has been proved that inflammation is an abnormal component of complications of obesity, metabolic syndrome, type 2 diabetes mellitus, atherosclerosis, cardiovascular diseases [26–28]. Inflammation participates in pathogenesis of development of insulin resistance, and pro-inflammatory cytokines — TNF-α, TNF-β, IL-6, C-reactive protein, etc. serve as the predictors of vascular complications of diabetes mellitus. Biochemical markers of inflammation (TNF-α, 2nd type of soluble TNF- α receptor, IL-6, C-reactive protein and soluble intercellular adhesion molecule of type 1) reduces sensitivity to insulin. Therefore, adipose tissue under PPARγ control completely determines relationship between pro-inflammatory cytokines and insulin resistance [25–28].

Due to the increased secretion of TNF- α and IL-6, visceral fat has a pro-inflammatory effect. These pro-inflammatory cytokines activate response transcription factor to the oxidative stress F-κB [25-28]. Currently, pro-inflammatory cytokine TNF-α is considered as a main mediator of insulin resistance in adipose tissue. Excessive content of adipose tissue associated with an increased production of TNF-α that induces the development of insulin resistance, at the same time, the level of TNF-α correlates with its degree and severity [29]. Excess of the adipose tissue upon obesity leads to its infiltration by immune cells and remodelling that provokes inflammation in it [24–27]. Release of pro-inflammatory cytokines stimulates lipolysis and induces insulin resistance leading to dysfunction of adipose tissue and systemic metabolic disorders. Inflammatory cytokines may independently induce insulin resistance by the direct action at the stage of post-receptor interaction of insulin or via adipose tissue. Mechanism of action of TNF- α on sensitivity to insulin involves the reduction of activity of tyrosine kinase of insulin receptor and increase of phosphorylation of serin IRS 1 — substrate of insulin receptor, as well as inhibition of expression of intracellular glucose transporters (GLUT 4) in fatty and muscular tissue. Furthermore, TNF-α may reduce a signal directly through PPARγ-activated receptors [24–29].

Discovery of the fact of increased content of TNF-α in adipose tissue as the inductor obesity-associated insulin resistance meant a new era in understanding of inflammation as the mechanism forming the base of metabolic dysfunction that precedes type 2 diabetes mellitus [26–29]. For example, S.Tsai et al. [29], consider obesity-associated insulin resistance and type 2 diabetes mellitus as the chronic inflammatory process of autoimmune origin, since the development and course of these disease is accompanied by infiltration of fatty tissue by macrophages and other cells of immune response.

Another cytokine produced by adipose tissue — TNF-β — is expressed both in immune and non-immune cells, including endothelial cells, fibroblasts, and adipocytes. Increased content of TNF -β in the blood serum is combined with obesity, insulin resistance, increased concentration of C-reactive protein and IL-6, as well as activation of apoptosis [22–29]. It has been established that the release of TNF-β from cells of adipose tissue is equivalent to its release from monocytes or macrophages. Increased TNF–β gene expression in animal adipocytes and upon obesity in human is accompanied by the increase of the degree of insulin resistance intensity. This allowed to conclude that this cytokine is one of the key mediators of its development. This anti-insulin action of TNF -β is a result of its effect on the reduction of GLUT 4 expression and inhibition of tyrosine kinase of insulin receptors in target cells and tissues [22–29].

Concentration of pro-inflammatory cytokine IL-6 grows up proportionally to the increase of adipose tissue mass in the blood [22–29]. Furthermore, adipose tissue is the place of secretion of other biologically active substances, including acetylation-stimulated protein (ASP). It is considered that ASP participates in the formation of inflammation, since it is formed as a result of interaction between several factors of complement, such as factor C3, factor B, and factor D (adipsin) [27–28]. The role and biological value of ASP in inflammation has not been completely studied.

Other hormones of adipose tissue which gene expression is regulated by PPARγ play a

certain role in inflammation. For example, it was proved that a reduced level of adipocytokines-adiponectin and leptin upon PPARγ dysfunction predisposes to the increased susceptibility to infections due to the reduced activity of T-cell immunity [22–29]. The most potent anti-inflammatory role among known cytokines is ascribed to adiponectin. It is supposed that synthesised adiponectin will provide competition for antibiotics and other antiinflammatory agents [27–29].

Visfatin hormone synthesised by visceral adipocytes is a acute phase inflammatory protein and it is sharply increased in case of acute damage syndrome of the lungs, kidneys and other organs. At the same time, visfatin may have an anti-inflammatory role, since in case of PPARγ activation it inhibits neutrophil-activated apoptosis. Mechanism of visfatin action in the inflammatory focus has not been studied completely, however, the range of authors consider that visfatin is a immune regulator with pronounced anti-inflammatory properties [22–29]. Such adipokines secreted by the adipose tissue as vaspin, apelin and omentin, inhibiting inflammatory response pathway, also have proinflammatory activity. Their favourable effects on inflammation, homeostasis of glucose and protective effects in respect to the small vessels and cardiovascular system have been found, however, mechanism of their action has not been studied completely [22–29].

Role of PPARγ and its ligands in case of bacterial infections predominantly involves its pro-inflammatory and antiinflammatory effects via inhibition of synthesis of pro-inflammatory molecules, such as L-1, IL-6, IL-10, IL-12, TNF-α, TNF-β, NF-kB, AP-1, etc., and activation of PPARγ-mediated modulation of phagocytosis, efferocytosis (disposal of dead cells by phagocytes, dendrite and epithelial cells, fibroblasts, etc.), as well as autophagy [7–11, 26–29].

At the stage of acute inflammatory process, "classically activated" by infectious agent, macrophage (M1) is characterised by increased phagocytic activity of foreign bodies and reduced activity of efferocytosis, increased production of pro-inflammatory cytokines, reactive oxygen species (ROS) and nitrogen oxide (NO) [46, 50]. This M1 programming takes place as a result of its stimulation by lipopolysaccharides (LPS) of bacteria, viruses, fungi, as well as natural cytokine interferon gamma (IFN-γ) and IFN-α or IFN-β. PPARγ activation by pro-inflammatory cytokines IL-4 and IL-13 is accompanied by the re-programming of macrophage from M1 to M2 — "alternative activation" with an increased synthesis of anti-inflammatory cytokines and activation of phagocytosis [50]. Simultaneously, adiponectin "bridges" are formed on M2 surface for recognition of death cells and activation of efferocytosis for their disposal (Fig. 2).

Clear evidence of the protective role of PPARγ and its agonists (troglitazone, etc.) in case of bacterial and viral infections was provided [22–23]. At the same time, it was shown

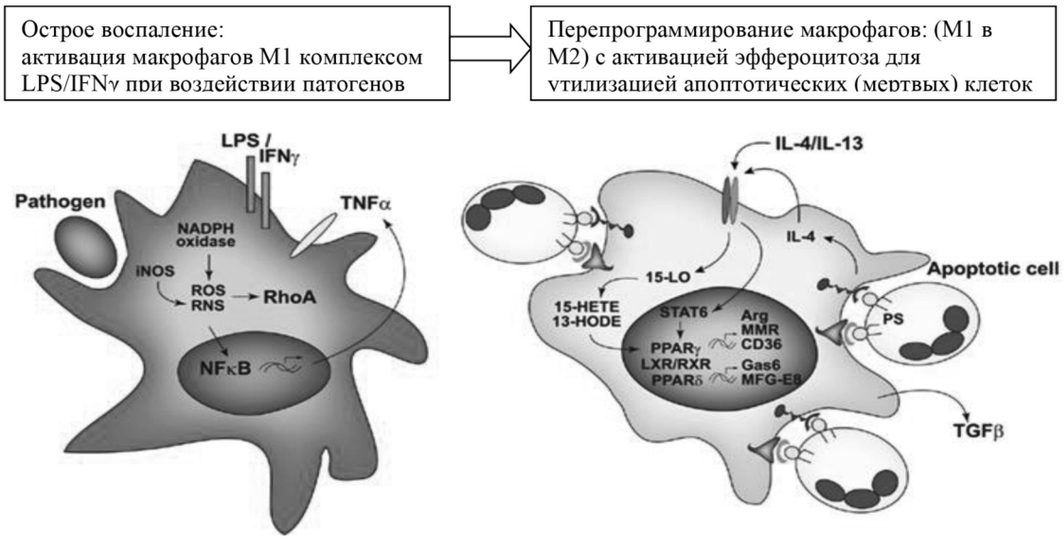

Fig. 2. Role of PPARγ activation in reprogramming of macrophages (M1 into M2) with an increased activity of phagocytosis, efferocytosis and synthesis of pro-inflammatory cytokines [50].

that PPARγ overactivation may activate caspase-dependent apoptosis in white blood cells, macrophages and lymphocytes that may diminish immune response. Furthermore, PPARγ activation may inhibit the migration of neutrophils and their adhesion, and also increase swelling of tissues by the local increase of expression of chemokines, cytokines and increase of the amount of mucin-producing cells [11, 23, 47–50]. Some bacteria are able to modulate PPARγ functions. Mycobacteria, such as a causative agent of tuberculosis and leprae, use lipids of hosts for intracellular surveillance and replication. It was shown that long-term administration of PPARγ agonists — antidiabetic drugs (thiazolidinediones) during 4–5.5 years increases the risk of pneumonia, bronchitis and other inflammatory processes [22–23] in patients, forming condition of "depleted receptor".

PPARγ dysfunction under the exposure to pesticides and other xenobiotics is accompanied by the impaired function of adipose tissue that is characterised by the reduced sensitivity to insulin, obesity, type 2 diabetes, hypoxia, intracellular oxidative stress, activation of autophagy, apoptosis and, undoubtedly, development of inflammation [22, 25–29, 50, 76–77]. These abnormal metabolic processes, in its turn, maintain the formation of chronic inflammation upon the long-term exposure to xenobiotics, impairing function of both PPARγ, as well as α and β [66–79].

At the same time, it was shown that PPARγ activation (pioglitazone, ciglitazone, troglitazone) aggravates inflammatory damage of the liver induced by conconvalin A (Con A, 20 mg/kg) due to intensification of caspase-dependent apoptosis and inhibition of translocation of nuclear factor NF-kB — suppressor of apoptosis [42]. Therefore, PPARγ antagonists may be used for management of hepatic damages, as apoptosis inhibiting agents.

Therefore, PPARγ are two-edge sword, depending on polymorphism or dysfunction having both pro- and antiinflammatory effect. Along with useful, it may also have negative effect on the body defence against pathogenic bacteria and viruses. Adjustment of the dose and time of administration of PPARγ agonists or antagonists in case of inflammation will be undoubtfully useful for achievement of the most desirable result.

PPARγ and carcinogenesis. Role of PPARγ in carcinogenesis is controversial. This receptor is extensively represented in different types of cancer cells of the breast, prostatic gland, liver, large intestine, lungs, and other organs [14–20, 30–31]. Upon addition of PPARγ ligand-activators to the cultivated cell lines obtained from these types of tissues, this receptor inhibits growth and cellular proliferation, and induces cellular death suggesting PPARγ role as a tumour suppressor. In animal models with induced carcinogenesis, PPARγ agonists inhibit tumour growth in different organs [16–18, 20, 30–31]. At the same time, it was noted that PPARγ agonists may stimulate tumorogenesis. For example, it was noted that PPARγ ligands increase the number of polyps in the intestine in case of family adenomatosis [19]. Inhibition of carcinogenesis in different organs upon PPARγ activation takes place predominantly due to the induction of autophagy [16–18], and to a lesser extent — due to activation of apoptosis, mainly at the dose level 5–10-fold higher compared to those, required for complete PPARγ activation [14, 30]. Induction of autophagy in cancer cells with PPARγ ligands (troglitazone) is accompanied by the development of vesicles with acidic hydrolases in cytoplasm that are one of signs of autophagy with increased expression of hypoxia-inducing factor 1α (HIF1A) and mitochondrial protein 3 (BNIP 3) [14]. Previously it was shown that known antitumour drugs — rapamycin, tamoxifen, and histone deacetylase inhibitors also cause autophagic death of cancer cells suggesting that induction of autophagy is an important mechanism of action of antitumour agents. Along with the induction of autophagy, activated PPARγ regulate gene expression that control angiogenesis (angiopoietin-like factor 4, hypoxia-inducing factor 1α, mitochondrial protein BNIP 3, etc.) which inhibit cellular growth and their proliferation, slow down metastasis, and also induce death of different types of cancer cells [14–21].

In recent years, relationship between the risk for cancer development and PPARγ dysfunction accompanied by the development of metabolic syndrome, obesity and hypovitaminosis, in particular — vitamin D deficiency, especially the risk for breast cancer development, was justified [26, 32–36]. This relationship is based on the ability of adipose tissue of

the breasts to increase local concentration of oestrogens activating proliferation via peripheral aromatization of androgens, as well as on mitogenic effect of insulin and insulin-like growth factor (IgF) on tumour epithelium. In its turn, vitamin D reduces the risk of cancer and its progression due to anti-insulin action — blockade of its mitogenic effect. D hypovitaminosis is characterised by the development of insulin resistance and compensatory hyperinsulinaemia. It was shown that D hypovitaminosis increases the risk for the development of hyperinsulinaemia, obesity and cancer, therefore, anticancer properties are inscribed to this vitamin [32–36].

Mechanism of carcinogenesis under conditions of hyperinsulinaemia is associated with malignant transformation of cells due to genetic mutations occurring at the background of hyperproiferation and inhibition of apoptosis. Insulin contributes not only to the development of a tumour, but also to the progression of its growth due to the presence of insulin receptors on the membranes of both normal and tumour cells. Insulin binding to insulin receptors induces signal pathways of mitogen-activated protein kinase (MARK) and phosphatidyl inositol-3-kinase (RISK) that leads to the transition of cells from g1 period to S period of cellular cycle, proliferation, ad inhibition of apoptosis of cancer cells [36–40].

Increased risk of cancer development in case of obesity is also associated with the ability of adipose tissue to play auto-, para-, and endocrine role under PPARγ control via secretion of the large amount of substances which action shows different biological effects, including both potentially carcinogenic and anticarcinogenic [30,31,40–45]. Biological substances — adipocytokines which are produced under PPARγ control by the cells of white adipose tissue participates in the regulation of cellular metabolism, processes of proliferation, autophagy, and apoptosis [26–29]. Leptin, tumour necrosis factor α (TNF- α) and interleukin 6 (IL-6) play an important role in development and progression of cancer, while adiponectin and vitamin D show anticarcinogenic effect [26–29, 32–39].

At the same time, it was found that leptin plays a multifactor role in tumorogenesis depending on PPARγ function. It was shown that it stimulates proliferation, migration, and invasion of cancer cells, and also inhibits apoptosis through MARK, STAT 3 and RISK signal pathways upon breast cancer [37].

TNF-α, a proinflammatory cytokine which expression in macrophages, lymphocytes and adipocytes is also regulated by PPARγ, plays an important role in tumorogenesis. Previously it was believed that TNF- α secretion causes tumour necrosis, however, in recent years its role in carcinogenesis was reassessed [27–38]. It was established that this cytokine actively participates in the induction of carcinogenesis and tumour progression. TNF-α stimulates formation of cyclooxygenase-2 (COX-2) — enzyme participating in synthesis of prostaglandins that activate epithelial growth factor, endothelial growth factor and IGF-1, stimulating cellular proliferation [38]. In its turn, pro-inflammatory cytokine IL-6 which in physiological conditions is produced by macrophages and T-lymphocytes, and in case of obesity — by adipocytes, inhibits tumour growth at early stages, and activates cellular proliferation and carcinogenesis at advanced stages [28, 29].

At the same time, adipocytokine adiponectin that possesses not only anti-inflammatory and insulin sensibilising action, also shows anticarcinogenic effect [27, 29, 40]. Mechanism of its anticarcinogenic action is associated with activation of adenosine monophosphate-activated protein kinase that leads to the delay of cells in Ig-1 phase of the cellular cycle, suppression of proliferation and activation of apoptosis, as well as the reduction of production of reactive oxygen species, slowing down of MARK activation, inhibition of cellular proliferation and inhibition of angiogenesis in tumour [39]. PPARγ dysfunction under the exposure to xenobiotics, including pesticides is accompanied by hypoadiponectinaemia which increases the risk for development and progression of both inflammation and cancer [27, 31, 32, 39, 40].

In recent years, the range of studies that explored efficiency of PPARγ agonists in combination with other chemotherapeutic agents in management of cancer was performed [43, 33]. Increase of therapeutic action and effect of high synergism following administration of PPARγ agonists (lovastatin — HMG-CoA inhibitor and troglitazone — PPARγ agonist) upon management of cancer of the breast, intestine, lungs, prostatic gland, neuroblastoma, and other malignant diseases [44], how-

ever, activation of tumorogenesis is observed in individual cases [45, 46].

Therefore, PPARγ activation inhibits carcinogenesis, and defective PPARγ or the reduction of their function under the exposure to xenobiotics, including pesticides, will undoubtedly contribute to the development and progression of cancer. PPARγ agonists not only inhibit tumorogenesis, but also remodel microenvironment of the tumour, slow down metastasis — penetration of cancer cells into the blood reduces due to the increased activity of metalloprotease inhibitors. Furthermore, PPARγ agonists enhance anti-proliferative action of anti-tumour agents. For example, rosiglitazone enhances anti-proliferative effect of gefitinib — inhibitor of epidermal growth factor in the culture of tumour cells [43], as well as anti-tumour preparations of platinum. Combination of the effect of PPARγ agonist troglitazone and lovastatin (NADP-dependent hydroxymethyl glutaryl-CoA-reductase) is also accompanied by more potent inhibition of the cellular growth of pulmonary adenocarcinoma [44]. Anti-tumour effect of PPARγ agonists was found in case of prostate cancer due to the increase in apoptotic activity and reduction of invasiveness [45]. A new PPARγ agonist — efatuazon was 500-fold more efficient compared to the combination of troglitazone and anti-tumour agents for management of oesophageal cancer. Possible relationship between PPARγ polymorphism and the risk for cancer development is reported [45]. It was shown that consumption of red meat and animal fats show stimulating effect on the growth of cancer, especially under conditions of PPARγ polymorphism [45].

Therefore, activated PPARγ has anti-proliferative effect in carcinogenesis, reduces the intensity of angiogenesis and metastases of cancer cells. Application of PPARγ agonists in combination with anti-cancer agents increases treatment efficiency. However, it is required to continue studies regarding clarification of clinical and biological role of PPARγ and its agonists in carcinogenesis and its application as a therapeutic target. In this regard, evaluation of changes in PPARγ function, as well as exploration of the levels of secretion of such adipokines as leptin and adiponectin should be undoubtedly conducted upon the study of toxic properties if xenobiotics and forecasting of their carcinogenic risk.

PPARγ and reproductive system. All isotopes of PPARs family (α, β and γ) are represented in the structures of hypothalamus-pituitary axis, and they actively participate in the functions of reproductive system [46, 51–65]. For example, all three PPAR isotopes may inhibit transactivation of oestrogenic receptors due to competitive binding to promotor zone of these receptors that may lead to infertility [46–49, 51–55]. In ovarian follicles, PPARγ inhibits expression of aromatase due to inhibition of NF-kB signalling pathway [51, 54, 55]. Furthermore, PPARγ agonist rosiglitazone is able to stimulate the expression of the range of enzymes participating in steroidogenesis [46]. It was noticed that PPARα agonist inhibit gene expression of enzymes that participate in synthesis of oestrogens in ovaries, and that obligatory condition for inhibiting effect to synthesis of oestrogens includes normal function of PPARα [51, 61], furthermore, all PPAR isotopes participate in the development of their secretion [51, 54, 55, 61].

All three PPAR isotopes regulate gametogenesis, ovulation, regression of corpus luteum, and process of implantation of fertilized ovum [51, 52, 59]. All three PPAR isotypes (α, β and γ) are also actively represented in male genital organs, regulate development of Sertoli cells, as well as gene expression, providing energy homeostasis of spermatogenesis and synthesis of testosterone [49 53, 56] (Fig. 3 and Fig. 4). PPARγ regulates synthesis of progesterone. This effect depends on the cell type, stage of their differentiation and stage of ovarian cycle [51, 54, 55]. PPARγ agonists increase secretion of progesterone and activity of 3-beta-hydroxysteroid dehydrogenase (3-beta-HSD) at the beginning and middle of lutein stage upon concomitant reduction of activity of prostaglandin-endoperoxide-synthase 2 (PTGS2) and synthesis of prostaglandin F2α. Effect of specific PPARγ antagonists cause opposite effect.

Dependence of gene expression of all three PPAR isotopes in endometrium from the stage of estral cycle and terms of pregnancy was detected — more pronounced increase of the levels of PPARγ m\RNA at day 13–15 of estral cycle and reduction of PPARβ at day 11–12 of pregnancy [61]. Furthermore, PPARβ agonists affect secretion of progesterone (P4) and 17β-estradiol in corpus luteum during pregnancy [62].

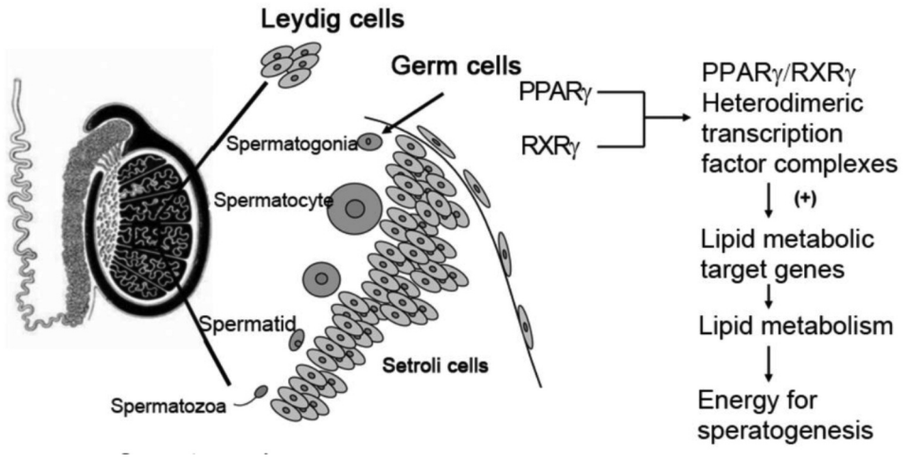

Fig. 3. Role of PPARγ in the provision of energy homeostasis [56].

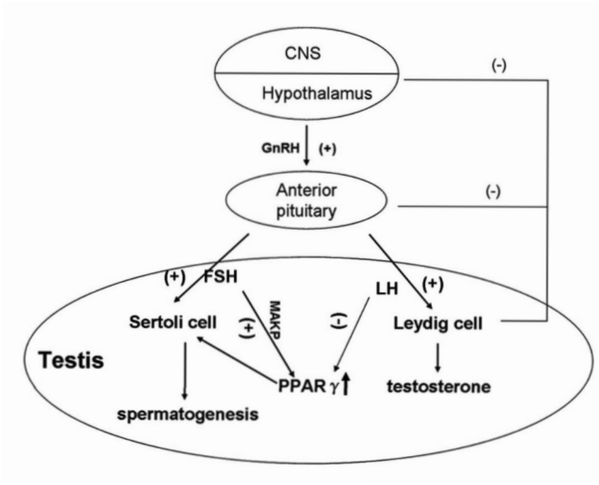

Fig. 4. PPARγ activation increases activity of spermatogenesis and synthesis of testosterone, regulating function of hypothalamus-pituitary axis [56].

It was established that all three PPAR isotopes play an important role in implantation of embryo. PPARs activation accelerates maturation of blastocysts, modulates secretion and activity of gonadotropin, and also maintains balance of luteinizing and follicle-stimulating hormones [51, 52, 65]. Each of all three PPARs plays its own physiological role in maturation of germ cells and development of embryo [51, 59]. Synthetic PPARγ ligands were recently applied for induction of ovulation in females with polycystic ovaries suggesting an important role of PPARγ in reproduction [60, 63]. On the other hand, pesticides, herbicides in particular, carbamates, etc., as well as plasticizers, components of personal hygiene products acting as chemical obesogens, are able to change PPARs function that is accompanied by the impairment of energy homeostasis, stimulation of lipogenesis and adipogenesis, development of obesity and type 2 diabetes [67-70, 72, 74-79]. These endocrine disruptor impair ovarian or testicular function, reduce quality of germ cells and negatively impact the development of embryo [49, 51, 56, 67-69].

Particular PPARγ role is assigned in formation and development of ovarian follicles, uterus, and placenta [51, 52, 54–55]. Placental expression of PPARγ increases after implantation and in the middle of the second trimester of pregnancy. Inactivation of PPARγ leads to the disorders in claustrophobia development, early embryonal mortality and severe developmental defects of placenta. Impairment of PPARγ function is accompanied by hormonal imbalance and premature miscarriage [62]. PPARγ agonists are used in complex therapy of impaired ovarian cycle and placental dysfunction, modulating their condition [51, 60].

Particular role of PPARγ in ovarian dysfunction is associated with impaired energy homeostasis, dyslipidemia, insulin resistance, obesity, and hyperandrogenaemia [49, 51, 56, 58]. These factors are also associated with a formation of polycystic ovaries upon PPARγ dysfunction or its polymorphism [64, 65].

All PPAR isotopes participate not only in the development of follicles but also in synthesis and metabolism of steroid hormones. For example, PPARα regulates synthesis of 17β-hydroxysteroid dehydrogenase IV (17β-HSDIV) — enzyme that catalyses transformation of 17-oestradiol into oestrone, its inactive form [51–52]. PPARα activation reduces expression

and activity of aromatase or oestrogen-synthase, limiting the rate of transformation of androgens into oestradiol. PPARγ activation increases secretion of progesterone, but decreases secretion of androstendione and testosterone due to the reduced activity of 17-hydroxylase and other enzymes, and has no effect on oestradiol secretion [51–52]. PPARγ reduces synthesis of androgen progenitors and, therefore, its dysfunction leads to the development of such disorders as polycystic ovarian syndrome, hyperinsulinism, disorders of ovulation, hirsutism, etc. [51–56]. In their turn, PPARγ agonists reduce biosynthesis of androgens [27, 51].

Special role in the development and functioning of reproductive organs is played by adipocytokines- hormones of adipose tissue, synthesis of which in adipocytes is regulated by activated PPARγ [27, 51, 56]. The effect of adipocyte hormone leptin on the reproductive system was the most studied. It was shown that leptin deficiency associated with the presence of gene mutation encoding molecule of hormone — leptin or gene encoding leptin receptor due to their congenital polymorphism or acquired dysfunction under the exposure to xenobiotics, leads to the impairment of functions of hypothalamus-pituitary-gonad axis.

Leptin is secreted by placenta and ovaries suggesting its important role in regulation of reproductive system [27, 56]. Leptin receptors were found at the surface of granulous cells, theca cells, and interstitial cells of ovaries. It was established that leptin inhibits processes of steroidogenesis in granulous cells and theca cells showing antagonistic properties in respect to insulin-like growth factor 1 (IGF-1), insulin, luteinizing hormone and transforming growth factor beta (TGF-β) [27, 56]. Furthermore, high concentrations of leptin inhibit the development of dominant follicle, impair ovulation, and contribute to the formation of polycystic ovarian syndrome [27, 51, 56]. At the same time, PPARγ hypofunction leads to the significant reduction of leptin level. Existent critical level of leptin is required for launch of natural algorithms in reproductive system. Upon low leptin level, amenorrhoea may develop suggesting ability of female body to stop ovulation process upon the reduction of adipose tissue mass, i. e., insufficiency of energy reserves [51].

Certain role in reproductive system is played by adipokine — adiponectin. Its increased concentrations inhibit formation of testosterone in ovaries, and reduced ones — contributes to the development and chronization of inflammatory processes [27, 51, 56]. In turns, increased concentrations of hormone — adipocytokine resistin increase synthesis of testosterone in ovaries [27, 51, 56] (Fig. 5).

Furthermore, PPARγ regulates active production and metabolism of steroids in adipose tissue that is provided by the activity of aromatases allowing conversion of fraction of circulating androgens (androstendione and

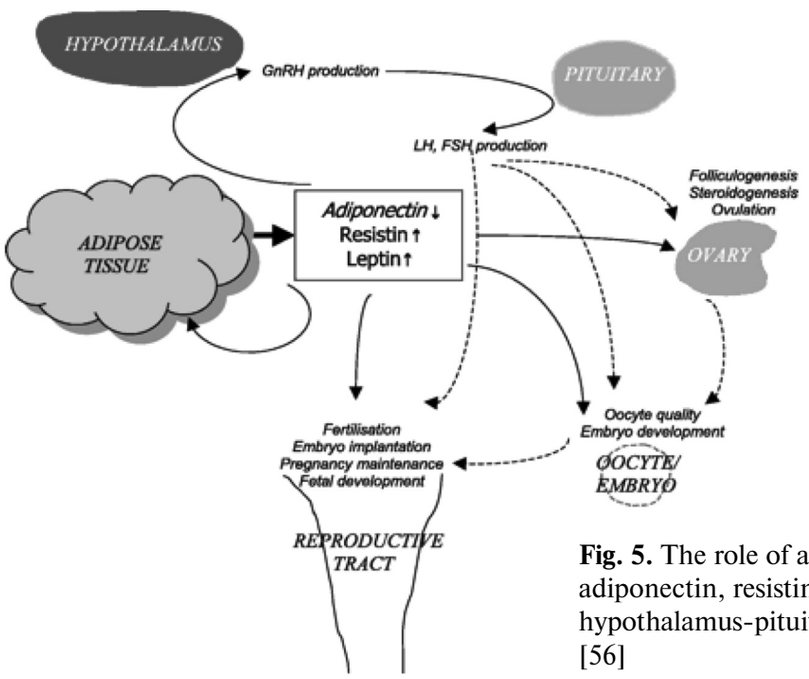

Fig. 5. The role of adipocytokines — adiponectin, resistin and leptin in functioning of hypothalamus-pituitary-gonad axis in females [56]

testosterone) into oestrogen (oestrone and estradiol, respectively) [51, 56]. Furthermore, the third part of circulating oestrogens is formed this way. Degree of aromatization significantly correlates with the fat mass. As in plasma, concentration of sexual hormones in adipose tissue reduces with the age. Due to the important role of adipose tissue hormones in reproductive system, the search for ways of therapeutic correction of impaired adipokine secretion in case of management of different reproductive conditions is topical.

PPARγ plays an important role in the development and functioning of the breast. In mice with blocked PPARγ, there is a lack of breast and milk fat development [51–52]. PPARγ plays a special role during lactation. Its dysfunction is accompanied by the reduced milk secretion and contributes to tumorogenic effects. Expression and physiological role of PPARγ, as well as PPARα and β in reproductive system of females is provided in Fig. 6.

Considering the important role of PPARγ and other isotopes in regulation of energy

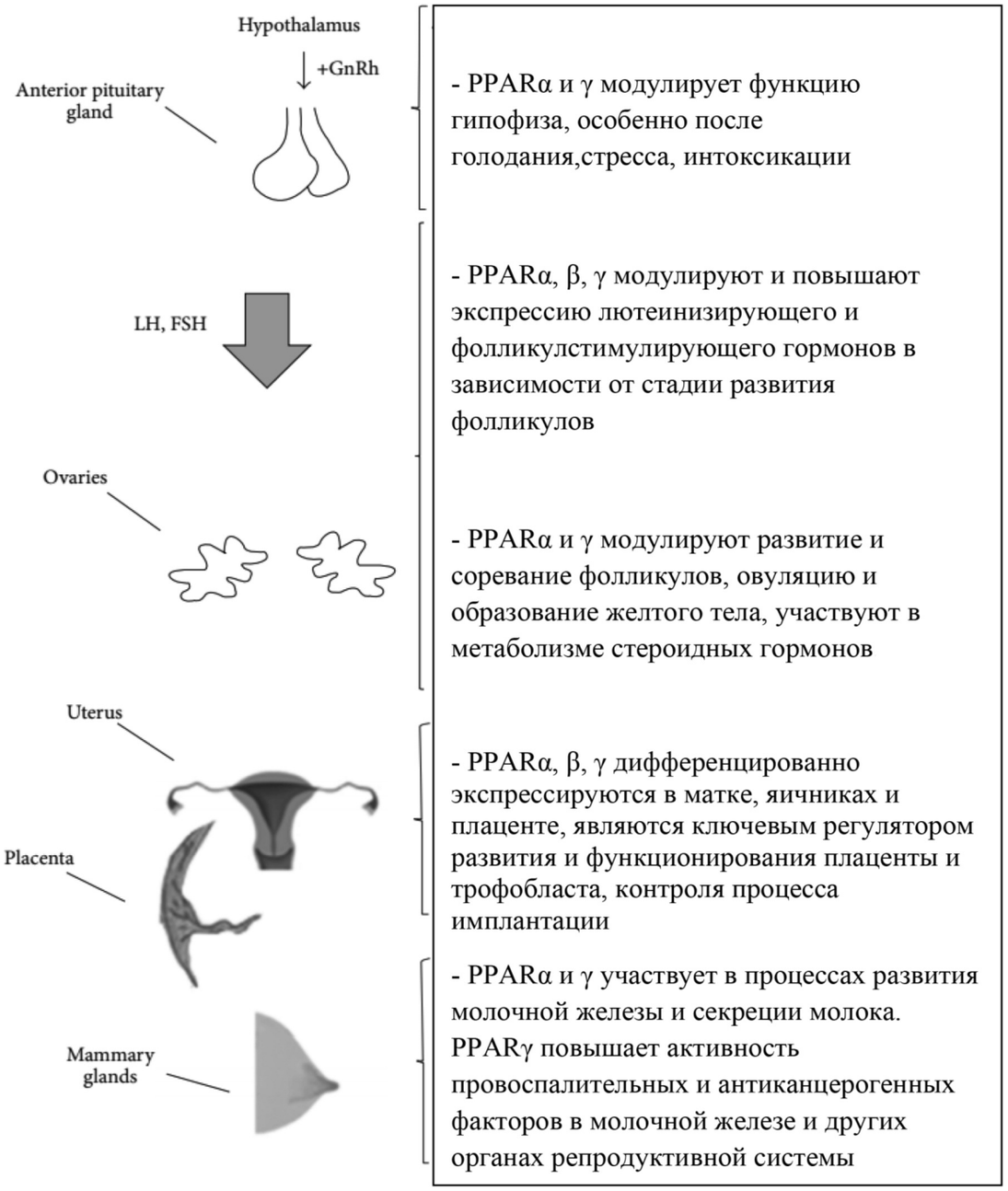

Fig. 6 PPARs expression and physiological role in the functioning of reproductive system, M.Vitti et al.[46], updated.

homeostasis and functions of reproductive system, interest of researchers regarding the use of agonists in restoration of metabolic homeostasis in females with ovarian dysfunction and other disorders of reproductive function grows [51–52, 60, 63].

Summarizing the results of literature data on the biological role of PPARγ in the body, we can make a conclusion on a key role of this receptor in differentiation of adipocytes, lipogenesis, accumulation and metabolism of lipids, balance of glucose and normalization of sensitivity to insulin, as well as the regulation of anti-inflammatory, antioxidative, antifibrotic, and anti-carcinogenic effects. Fig. 7 provides almost all known effects of PPARγ activation. It should be noted that in recent years studies that suggest also an important role of PPARγ in the development and functioning of the reproductive organs occurred.

It was shown that PPARγ participate in the control of all functions of the reproductive system, and in case of DNA mutations encoding this receptor or acquired hypofunction, such processes as impaired conceiving, developmental defects, miscarriages, polycystic ovaries, endometriosis, fibromyoma, inflammatory processes and carcinogenesis occur. Formation of these processes is due to the dysfunction of PPARγ developed under the exposure to endocrine disruptor, and therefore — accompanied by activation of pro-inflammatory profibrogenic factors, inhibition of autophagy and efferocytosis, and also activation of proliferative reactions and development of carcinogenesis. Considering the important role of PPARγ in formation of homoeostatic processes in the body, PPARγ and its signalling pathways will be widely used as a targets upon management of diseases of different organs and systems.

Therefore, PPARγ is expressed universally — in all cells and organs, plays regulating role in the processes of energy homeostasis: in adipogenesis, lipogenesis, accumulation of fats and glucose homeostasis. PPARγ regulates secretory function of adipose tissue, controls and provides anti-inflammatory, anti-proliferative, anti-fibrogenic, and anti-carcinogenic effects

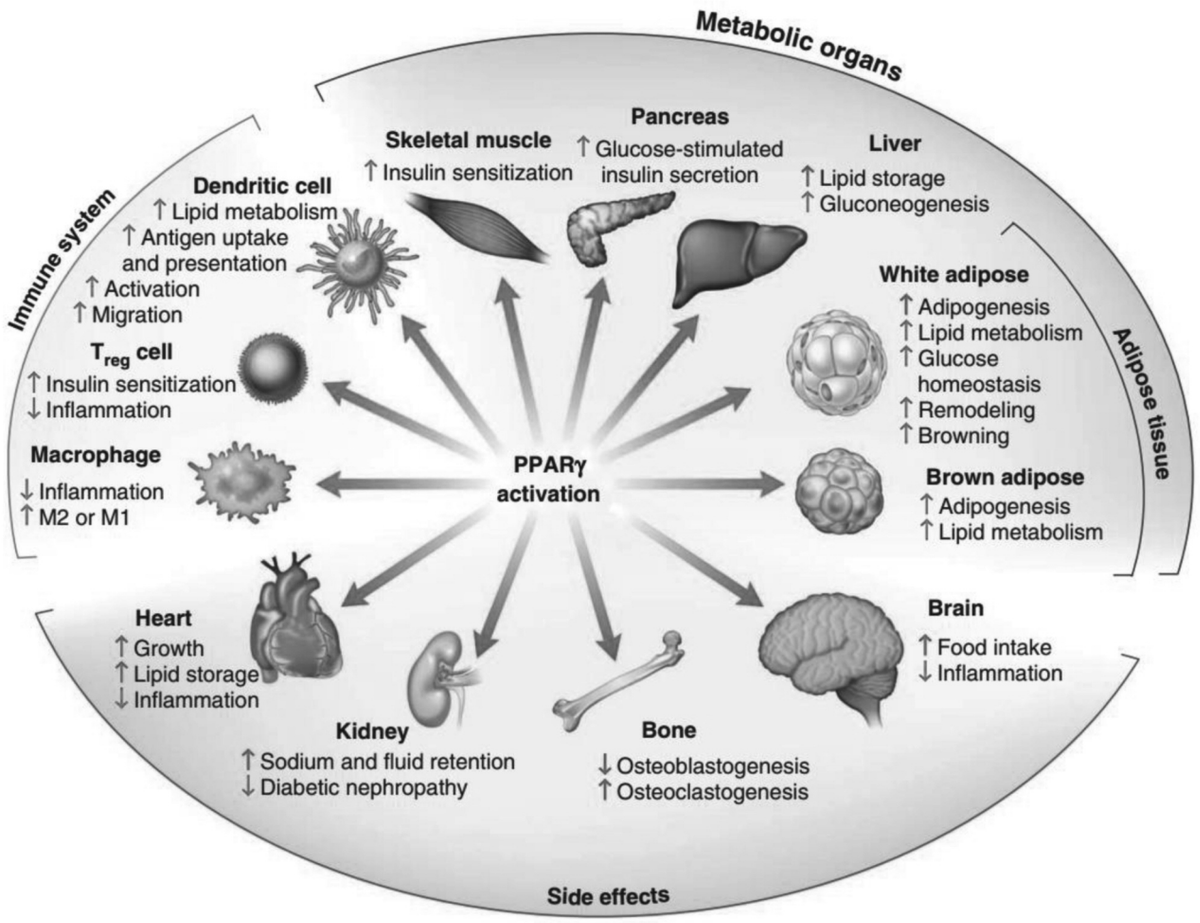

Fig. 7. Known effects of PPARγ activation [80].

in the body. Application of PPARγ agonists in complex therapy increases treatment efficiency in many conditions: type 2 diabetes mellitus, metabolic syndrome, obesity, inflammation, fibrosis, carcinogenesis, as well as in case of management of neurodegenerative diseases and conditions of reproductive system. A special interest is paid to the study of pathogenic mechanisms of exposure and effect of endocrine disruptor to PPAR family and their signalling pathways.

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