# 4 Nuclear Receptors in Energy Metabolism

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**Abstract**

Nuclear receptors are master regulators of energy metabolism through the conversion of extracellular signals into gene expression signatures. The function of the respective nuclear receptor is tissue specific, signal and co-factor dependent. While normal nuclear receptor function is central to metabolic physiology, aberrant nuclear receptor signaling is linked to various metabolic diseases such as type 2 diabetes mellitus, obesity, or hepatic steatosis. Thus, the tissue specific manipulation of nuclear receptors is a major field in biomedical research and represents a treatment approach for metabolic syndrome. This chapter focuses on key nuclear receptors involved in regulating the metabolic function of liver, adipose tissue, skeletal muscle, and pancreatic β-cells. It also addresses the importance of nuclear co-factors for fine-tuning of nuclear receptor function. The mode of action, role in energy metabolism, and therapeutic potential of prominent nuclear receptors is outlined.

**Keywords**

Energy homeostasis · Glucose and lipid metabolism · Nuclear receptor-based therapies · Metabolic syndrome · Transcriptional co-factors

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## 4.1 Introduction and Outline

Nuclear receptors govern multiple essential functions in metabolism. In the current chapter, we aim to introduce the most important nuclear receptor-related functions and factors in the organ-specific regulation of glucose and lipid



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metabolism, as well as diseases associated with their malfunction, and novel approaches to target them. Notably, there is a multitude of additional nuclear receptors, classified either as orphan receptors including the estrogen related receptor (ERR) and the retinoic acid related receptor (ROR), or with known ligands such as the estrogen receptor (ER), the androgen receptor (AR), and the retinoic acid receptor (RAR). These receptors are also involved to some extent in the regulation of metabolism, but cannot be covered exhaustively within the scope of this chapter. Our increasing understanding of the organ- and context-specific regulation of nuclear receptors and their co-factors (Box 4.1) has already led to the development of promising therapeutics for common diseases and will likely yield novel treatment approaches for metabolic diseases in the future. We here discuss the roles of the most prominent nuclear receptors in metabolism, PPARs, LXR, FXR, and GR, in the major metabolic organs and summarize the current state of play as regards therapeutic targeting of these receptors in metabolic diseases.

## 4.2 Liver

Constant food accessibility and an overly sedentary lifestyle have led to an obesity pandemic. The imbalance of energy availability and expenditure is detrimental especially for the liver, which is one of the central organs for metabolism. Consequently, conditions such as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are on the rise. To date, there are no efficient treatments for these diseases. Increasing knowledge of the diverse functions of nuclear receptors has led to growing interest in pharmacological compounds that can manipulate their activity. Tissue- or pathway-specific manipulation of nuclear receptors could represent novel treatment possibilities.

### 4.2.1 PPARα Is the Key to Liver Lipid Metabolism

Peroxisome proliferator-activated receptor alpha (PPARα) is a nuclear receptor highly abundant in liver and other tissues with high rates of fatty acid oxidation such as cardiac muscle, brown adipose tissue, and kidney [1–3]. PPARα was initially identified as an activator of peroxisome proliferation induced by hepatocarcinogens [4], but was since established as a master regulator of liver lipid metabolism. PPARα expression levels were found to be reduced in NAFLD patients, but increased in parallel with NAFLD histological improvements secondary to lifestyle intervention or bariatric surgery [5]. In line with this, hepatocyte specific disruption of PPARα in mice resulted in steatosis and steatohepatitis indicating an essential role in lipid utilization [6]. Indeed, PPARα expression is increased during suckling [7] and fasting [8], both states in which fat serves as the primary energy source. During fasting, fatty acids released from adipose tissue serve as endogenous ligands for PPARα and promote the activation of the majority of pathways involved in lipid catabolism, including lipid uptake, intracellular lipid trafficking, peroxisomal and mitochondrial β-oxidation, and ketone body synthesis. Cellular lipid uptake, which is the first step in lipid catabolism, is facilitated by the fatty acid transporters fatty acid transporter (FAT/CD36) and fatty acid transporter protein (FATP). Both are direct target genes of PPARα [9] highlighting the importance of PPARα function not only for hepatic cellular metabolism but also for fatty acid clearance from the periphery. Apart from lipid uptake, PPARα regulates medium-chain acyl-coenzyme A (CoA) dehydrogenase [10, 11] and acyl-CoA oxidase 1 [11] which are the rate limiting enzymes of mitochondrial and peroxisomal fatty acid β-oxidation (Fig. 4.1). These miscellaneous regulatory functions of PPARα in lipid metabolism sparked interest in developing compounds based on PPARα target gene products to counteract abnormalities and disorders associated with the metabolic syn-

**Box 4.1: Transcriptional Co-factors as Tissue- and Context-Specific Regulators of Nuclear Receptor Function**

The transcriptional control of biological processes requires tight regulation and the ability to rapidly adapt in response to metabolic changes. NRs facilitate the transcription of target genes ligand dependently, however also rely on the recruitment of co-factors. These co-factors either induce or suppress transcription and are referred to as co-activators or co-repressors, respectively. Co-factors are not exclusive to the NRs, however in general, unliganded NRs preferentially interact with co-repressors and thereby inhibit transcription while ligand binding promotes NR:co-activator interaction which facilitates transcription. Interestingly the transcriptional co-factors transducin β-like protein 1 (TBL1), and TBL-related 1 (TBLR1) were reported to act as so called "nuclear exchange factors", which regulate gene repression and expression by exchanging co-repressors and co-activators [147]. Co-factors modulate NR activity by determination of cellular localization, regulation of NR stability, or posttranslational modification of the NR itself or the chromatin [148–150]. One of the better studied repressor complexes is the NR co-repressor (NCoR) and silencing mediator of retinoic acid and thyroid hormone receptors (SMRT) co-repressor complex (NCoR/SMRT complex). This repressor complex is comprised of the core subunits NCoR or SMRT as well as histone deacetylase 3 (HDAC3), G-protein pathway suppressor 2 (GPS2), TBL1, and TBLR1 [151, 152]. Repression through the NCoR/SMRT complex is partly achieved by HDAC3 mediated deacetylation of chromatin, which disables transcription. HDAC3 is a negative regulator of white adipose tissue (WAT) browning [153], and a modulator of liver lipid metabolism [154] and pancreatic β-cell function [155, 156], indicating its prominent and tissue-specific function in molecular metabolic regulation. GPS2 regulates liver lipid metabolism [157] as well as adipose tissue metabolism and its endocrine function [158, 159]. Interestingly, while hepatocyte specific loss of GPS2 ameliorates NASH [157], TBL1 and TBLR1 loss of function in the liver promotes steatosis development [160], indicating that the complex core components regulate transcriptional events independently of NCoR and SMRT and/or through recruitment of additional regulatory units. In addition, TBL1 and TBLR1 were shown to directly interact with NRs and facilitate diverse tissue specific metabolic events including proliferation in pancreatic cancer cells [161, 162] and adipose tissue lipid metabolism [163]. It is currently estimated that the group of co-regulators includes around 150–400 proteins in humans [164], providing a unique tissue- and context-specific targeting opportunity in future research. As disruption of co-factor function results in various metabolic diseases, insights into the mechanistic action of these co-factors are essential. The diverse features of these co-factors and their ability to function as complexes but also independently highlight their importance for the maintenance of a normal and healthy metabolism and their potential in the development of novel therapeutic drugs.

drome. A recent prominent example which gained interest as a pharmacological target is fibroblast growth factor (FGF) 21 [12]. FGF21 administration reduced body weight, blood glucose levels, circulating plasma insulin, and hepatic gluconeogenesis in diet-induced and genetic mouse models of obesity, as well as in non-human primates [13–16]. Additionally, while FGF21 ablation resulted in severe hepatic steatosis and inflammation [17, 18], elevation of circulating FGF21 levels reversed fatty liver and NASH [18, 19]. Due to poor pharmacokinetic properties of natural FGF21, several modified FGF21 analogues were developed, which are currently undergoing clinical trials.

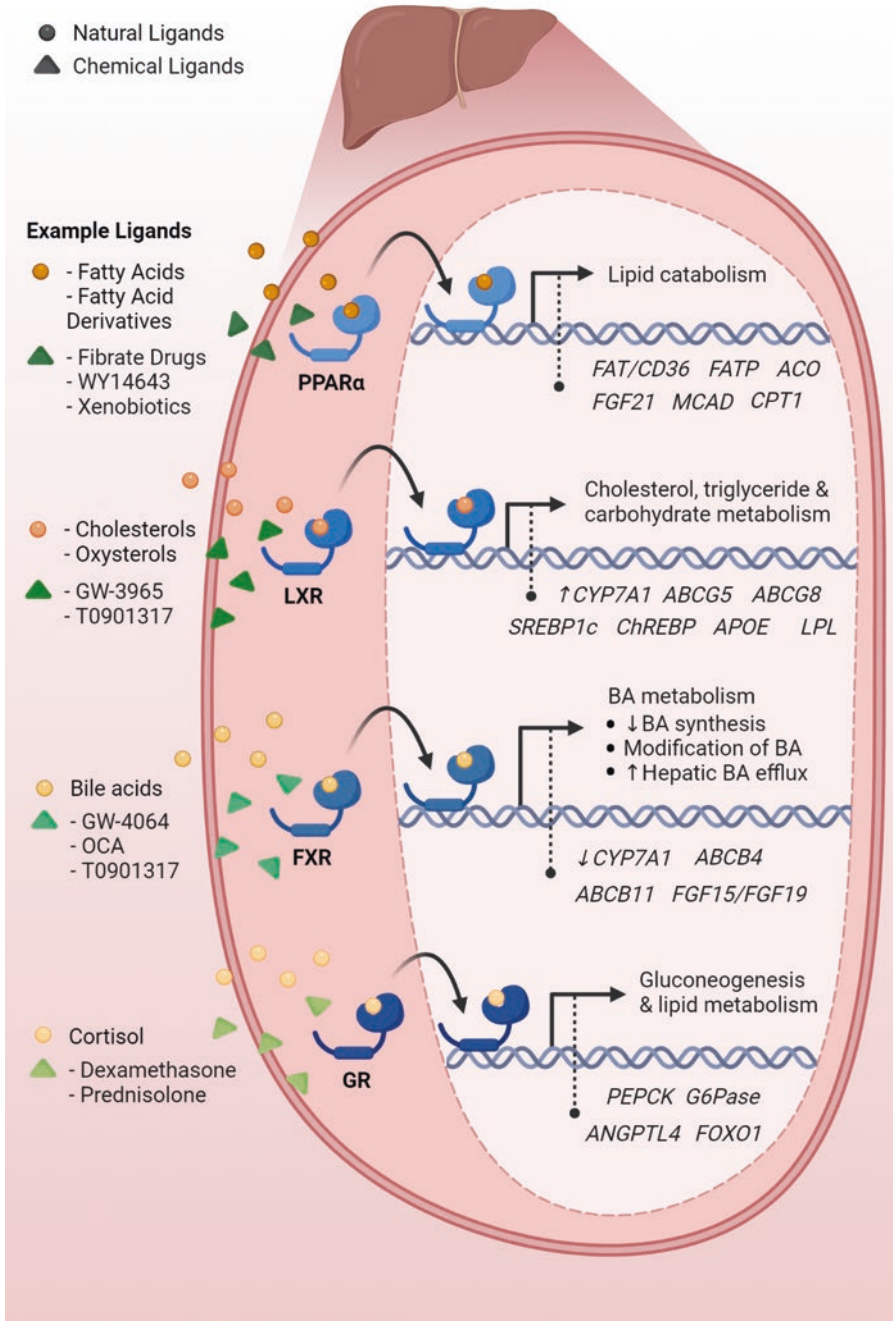


**Fig. 4.1 Nuclear receptors involved in regulating liver metabolism.** Schematic representation of the main functions of nuclear receptors in the liver and their ligands, main mode of action, and key target genes. (**a**) Upon ligand binding, PPARα induces lipid catabolism through direct induction of genes involved in cellular lipid uptake (FAT/CD36, FATP), fatty acid β-oxidation (ACO, MCAD, CPT1), and ketone body synthesis. (**b**) Apart from cholesterol metabolism (CYP7A1, ABCG5, ABCG8), LXR controls genes involved in carbohydrate (ChREBP) and triglyceride (SREBP1c, APOE, LPL) metabolism (**c**) FXR controls hepatic bile acid metabolism and is a known LXR counterplayer. (**d**) Glucocorticoid induced GR activity promotes gluconeogenesis (PEPCK, G6Pase) and lipid metabolism (ANGPTL4, FOXO1) in the hepatocytes. *FAT/CD36* fatty acid transporter, *FATP* fatty acid transport protein, *ACO* acyl-CoA oxidase, *MACD* medium-chain acyl-CoA dehydrogenase, *FGF21* fibroblast growth factor

Recently completed phase 2 studies assessed the efficacy and safety of FGF21 covalently conjugated to polyethylene glycol (PEGylation). PEGylated FGF21 significantly reduced hepatic fat, liver stiffness, fibrosis markers, and markers of liver damage [20, 21]. In contrast to recombinant FGF21 and other FGF21 analogues, PEGylated FGF21 did not induce bone loss or increased blood pressure in the pre-clinical setting [22–24], suggesting a low risk for chronic treatment in patients. Currently two phase 2b studies are ongoing, which evaluate the effects of PEGylated FGF21 in NASH patients with severe fibrosis (ClinicalTrials.gov Identifiers: NCT03486899 and NCT03486912). Another long-acting FGF21 fusion protein (Fc-FGF21) was shown to improve glucose metabolism and plasma lipid levels across species, including humans [25, 26]. Completion of a phase 2 clinical study, which investigated the effects of Fc-FGF21 in NASH patients, reported reduction of the hepatic fat fraction and markers of liver damage, while improving glycemic control [27], indicating the potential of this compound as a novel treatment possibility for NASH and NAFLD. The current lack of approved treatments for these conditions underlines the significance of the pharmacological improvements in obesity related morbidities after FGF21 analogue administration. As a direct PPARα target gene, this indicates how crucial the physiological function of PPARα in the liver is, and how promising manipulations of these pathways are to develop novel treatment possibilities for the metabolic syndrome and its manifestation as NAFLD and NASH.

### 4.2.2 LXR and FXR Are Regulators of Cholesterol Metabolism

The two liver X receptor (LXR) isoforms, α and β, are key regulators of cholesterol, triglyceride, and carbohydrate metabolism in the liver [28–30]. LXRα was initially discovered in the liver where it is highly abundant [31], whereas LXRβ is ubiquitously expressed [32]. Cholesterol, cholesterol derivatives, and cholesterol precursors were identified as natural LXR ligands indicating a central role of LXR in cholesterol metabolism [33]. Indeed, LXR is an intracellular cholesterol sensor and modulator by directly regulating genes involved in reverse cholesterol transport (RCT), conversion of cholesterol into bile acids, and intestinal excretion of cholesterol. In rodents, LXR induced cholesterol 7 α-hydrolase (CYP7A1) expression upon ligand binding, which is the first step and the rate-limiting enzyme for bile acid synthesis [28]. Interestingly, binding of bile acids to the farnesoid X receptor (FXR), another nuclear receptor highly abundant in the liver, downregulated CYP7A1 expression [34], identifying FXR as a LXR counterplayer. The downregulation of CYP7A1 was in part facilitated by the FXR target gene FGF15 in mice and its orthologue FGF19 in humans [35]. In addition to bile acid synthesis inhibition, FXR promoted the modification of bile acids into less toxic molecules [36] and hepatic bile acid efflux via ATP-binding cassettes ABCB11 and ABCB4 [37–39], while LXRα and β regulated cholesterol efflux from the liver into the bile via ABCG5 and ABCG8 [40] (Fig. 4.1).

Despite sharing 78% similarity in their amino acid sequence [41], LXRα and β do not possess identical functions in metabolism [42]. In mice lacking LXRα only, cholesterol removal from the body was severely impaired [28, 42], while LXRβ knockout (KO) mice were protected from such a phenotype [42]. Interestingly, LXRs were also identified to regulate glucose metabolism through energy utilization in brown fat [43], pancreatic insulin secretion [44], and direct upregulation of the glucose transporter GLUT4 in adipose tissue and muscle [30, 45, 46]. Additionally, ligand activated LXR activity inhibited the gluconeogenic program through

**Fig. 4.1** (continued) 21, *CPT1* carnitine palmitoyltransferase 1, *CYP7A1* cholesterol 7 α-hydrolase, *ABCG5* ATP-binding cassette G 5, *SREBP1c* sterol regulatory element-binding transcription factor 1, *ChREBP* carbohydrate-responsive element-binding protein, *APOE* apolipoprotein E, *LPL* lipoprotein lipase, *BA* bile acid, *PEPCK* phosphoenolpyruvate carboxykinase, *G6Pase* glucose-6-phosphatase, *ANGPTL4* angiopoietin-like 4, *FOXO1* forkhead box protein O1

down-regulation of peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC-1), phosphoenolpyruvate carboxykinase (PEPCK), and glucose-6-phosphatase (G6Pase) expression in the liver (Fig. 4.1). Suppression of gluconeogenesis was accompanied by increased glucokinase expression, which promoted glucose utilization and blood glucose clearance [30, 45, 47]. Similar to LXR, FXR also regulates glucose metabolism through fine tuning of gluconeogenesis. In the fed state FXR inhibited gluconeogenesis through repression of the key enzymes PEPCK and G6Pase [48, 49], while at fasted state FXR promoted the gluconeogenic program [49]. Accordingly, mice lacking FXR are prone to glucose intolerance and insulin resistance [50].

Due to the primarily beneficial action of LXR on glucose metabolism, LXR agonists were initially thought to be ideal therapeutic agents to treat hepatic steatosis and hyperglycemia. Indeed, LXR agonist administration suppressed the gluconeogenic program and thereby reduced blood glucose levels [45]. Some of the promising effects of LXR agonists on glucose metabolism were, however, shown to be rodent specific [51]. Additionally, synthetic LXR agonists promoted hepatic lipogenesis and steatosis, via transcriptional activation of the triglyceride master regulator sterol regulatory binding transcription factor (SREBP) 1 [29, 52]. Reduced lipogenesis was observed in LXRα KO mice in comparison to wild type mice [28]. However, LXR agonist administration in LXRα KO mice increased SREBP1 gene expression [29] indicating that both LXRα and LXRβ regulate lipogenesis and triglyceride synthesis in the liver. The species-specific effects as well as adverse effects of synthetic LXR agonists raised concerns as to the suitability of LXR agonists for lipid metabolism-associated disorders. In recent studies inverse LXR agonists gained interest for NASH/NAFLD treatment. Similar to agonists, inverse agonists bind to the same receptor, however they exert the opposite effect on the target cells. The inverse LXR agonist 10rr was found to inhibit lipogenesis by downregulating the expression of SREBP1, acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS) and stearoyl-CoA desaturase-1 (SCD-1) [53]. Interestingly, the liver specific inverse LXR agonist SR9238 exerts antifibrotic and anti-inflammatory effects on NASH [54, 55] and suppresses hepatic steatosis [56]. Surprisingly, in contrast to what was seen in LXR KO mice, reduced plasma cholesterol levels were observed, partly through downregulation of HMG CoA reductase (HMGCR) [56], a key regulator of cholesterol synthesis. So far, no studies were performed testing inverse LXR agonists in humans. However, administration or combination of such inverse agonists could provide novel implications and treatment possibilities in fatty liver associated diseases. In contrast, several FXR agonists already underwent clinical studies especially for the treatment of NASH. The FXR agonist obeticholic acid (OCA) reduced bile acid synthesis by repression of CYP7A1 gene expression. Moreover, OCA protected from NASH induced apoptosis of hepatocytes through suppression of p53 [57]. In NASH patients, treatment with OCA improved liver histology, however induced pruritus (itching) [58], which was also observed in treatment with other FXR agonists [59]. Currently a long term phase 3 study (NCT02548351) is ongoing to evaluate the effects of OCA on mortality, liver-related clinical outcomes, and long-term safety [60]. Cilofexor, another FXR agonist, was reported to improve hypertension and liver fibrosis in rats [61]. Additionally, in a phase 2 clinical trial NASH patients receiving cilofexor showed improved hepatic steatosis and liver transaminases [59]. In conclusion, FXR agonists represent novel and attractive candidates for NASH treatment. The current ongoing studies to determine safety and efficiency highlight the potential of such FXR agonists.

### 4.2.3 GR – Linking Inflammation and Metabolism

The glucocorticoid receptor (GR) is a hormone-dependent nuclear receptor which regulates a wide range of metabolic processes including inflammation, lipid and glucose metabolism. More than 50 genes are under direct GR control in the liver alone [62]. GR directly regulates the expression of the gluconeogenic key enzymes PEPCK and G6Pase, suggesting an essential role

of GR in gluconeogenesis. Thus, suppression of GR activity in the liver improved hyperglycemia and dyslipidemia in genetic and inducible models of diabetes through down-regulation of PEPCK and G6Pase [63–65] (Fig. 4.1). Apart from gluconeogenesis, GR was shown to control lipid metabolism by regulating enzymes involved in lipogenesis, triglyceride (TG) uptake and fatty acid β-oxidation, resulting in hepatic lipid accumulation upon GR activity [66, 67]. Conversely, upon liver specific GR dysfunction, hepatic steatosis in db/db mice was ameliorated mainly through the induction of hairy enhancer of split 1 (HES1) gene expression [67]. Additionally, hepatocyte-specific GR KO impaired systemic bile acid distribution, hepatic bile acid uptake, and increased the susceptibility to develop cholesterol gallstones [68]. This indicates the importance of functional and balanced GR signaling in the liver. Previous studies identified regulatory factors such as microRNAs, transcription factors, or co-factors that directly interact with GR and thereby fine tune and balance its actions in the liver and other tissues [69–72]. Pharmacological activation of GR through cortisone or dexamethasone has immune-suppressive properties and is therefore commonly used in inflammatory or auto-immune diseases [73], however the use is overshadowed due to its severe metabolic side effects. Chronic glucocorticoid (GC) administration and the induced GR activity can result in metabolic abnormalities including hyperglycemia, insulin resistance, hepatic dyslipidemia, and hypertension [74]. Despite these severe negative effects that come with chronic GR activation, GCs are still widely prescribed. Interestingly, it was previously shown that due to alternative splicing, GR is expressed as two isoforms, GRα and GRβ [75]. Both isoforms are ubiquitously expressed in most tissues, with GRβ to a lesser extent than GRα. Additionally, in contrast to GRα, GRβ lacks a binding pocket for GCs [75, 76]. GRβ was initially shown to act as a GRα antagonist by binding to glucocorticoid responsive elements without inducing gene expression and also through heterodimerization with GRα [75, 77–79]. However, recent studies suggest that GRβ has, apart from the GRα antagonizing property, distinct regulatory functions on gene expression. Animal studies revealed that GRβ is the main regulator of hepatic gluconeogenesis and lipid storage. GRβ gene expression was elevated in the liver upon diet induced obesity [80]. Moreover, upon liver specific GRβ overexpression, hepatic and serum TG levels were significantly elevated. Additionally, GRβ overexpression resulted in hyperglycemia without alterations in circulating insulin levels suggesting increased gluconeogenesis or reduced hepatic insulin signaling [80]. Interestingly, short term GC administration induced lipolysis in adipose tissue through transcription of hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) [81]. An explanation for this observation might be that short-term exposure to GC specifically activates GRα, which facilitates lipolysis [81]. GRα action however is antagonized by GRβ upon chronic GC administration [75, 77, 78] which in turn induces gluconeogenesis and lipogenesis [80], notably through interaction with PPARα pathways, finally resulting in metabolic disruptions such as hepatic dyslipidemia and hyperglycemia. Given the antagonizing effect of GRβ on GRα and the direct regulation of hepatic glucose and lipid metabolism by GRβ, differentiation between the isoforms is essential in future studies. Specific regulation of either of the GR isoforms thus might provide novel treatment possibilities or reduce the severity of GC-associated side-effects.

## 4.3 Adipose Tissue

The white adipose tissue (WAT) is the central organ for energy storage. Excess energy is converted into TG and stored in lipid droplets in adipocytes. In nutrient deprived states, fatty acids are released and serve as energy source for other tissues such as liver or skeletal muscle. Additionally, adipose tissue was identified as an endocrine organ and releases a wide range of adipokines which regulate immune responses, control blood pressure, or modify glucose homeostasis. Modern lifestyle but also genetic predisposition account for excessive fat storage in WAT, which is accompanied by hyperglycemia

and dyslipidemia. In contrast, brown adipose tissue (BAT) is specialized to dissipate chemical energy in the form of non-shivering thermogenesis. The ability of white adipocytes to convert into brown-like or beige adipocytes, named browning and partly regulated by nuclear receptors (see also Box 4.1), represents an intensively studied field to target lifestyle induced obesity.

### 4.3.1 PPARγ Is the Master Regulator of Adipose Tissue Function

The master regulator of adipose tissue function is PPARγ. Its expression is rapidly induced during adipogenesis [82], regulating hundreds of genes central to adipocyte function, including lipid transport (FABP4), fatty acid uptake (FATP, LPL), recycling of fatty acids (PEPCK), and lipolysis (GPR81) [83–87] (Fig. 4.2). Indeed, PPARγ KO in pre-adipocytes completely inhibited adipocyte formation [88], proving the vital importance of this nuclear receptor for adipogenesis. In patients, a mutation in the ligand-binding domain of PPARγ led to partial lipodystrophy and insulin resistance [89], and mice lacking PPARγ in the adipose tissue displayed the same phenotype [90]. Aside from the effects on adipogenesis, PPARγ is also important for insulin sensitivity as it regulates adiponectin and resistin expression [91, 92]. Synthetic PPARγ agonists, in particular thiazolidinediones, ameliorate insulin resistance and are widely used in type 2 diabetes mellitus (T2DM) treatment [93]. Fat accumulation in insulin sensitive tissues such as liver and skeletal muscle has been shown to promote insulin resistance. PPARγ agonist-induced upregulation of genes involved in fatty acid uptake and storage in the adipose tissue promotes redistribution, and could thereby prevent ectopic fat accumulation in liver or skeletal muscle. Weight gain, liver damage, and cardiovascular events are, however, common side-effects upon chronic PPARγ activation [94, 95]. Interestingly, in vitro exposure of white adipocytes and in vivo exposure of mice to synthetic PPARγ agonist induced expression of brown fat marker genes including uncoupling protein 1 (UCP1), PR

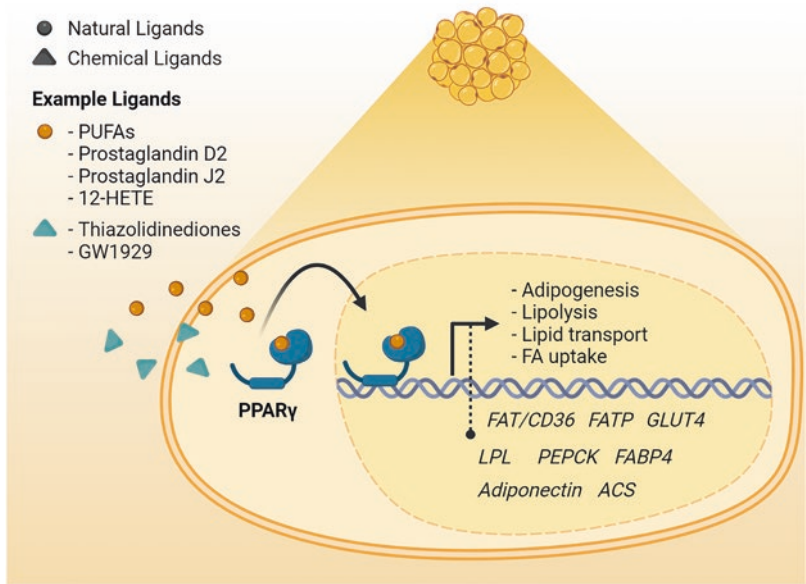


**Fig. 4.2 Regulation of adipocyte function by PPARγ.** Upon ligand binding PPARγ induces genes involved in adipogenesis, lipid transport (FABP4), fatty acid uptake (FAT/CD36 FATP), lipid recycling (PEPCK, GLUT4), and lipolysis (LPL). *PUFA* polyunsaturated fatty acid, *12-HETE* 12-hydroxyeicosatetraenoic acid, *FAT/CD36* fatty acid transporter, *FATP* fatty acid transport protein, *GLUT4* glucose transporter type 4, *LPL* lipoprotein lipase, *PEPCK* phosphoenolpyruvate carboxykinase, *ACS* acetyl-CoA synthetase, *FABP4* fatty acid-binding protein 4

domain containing 16 (PRDM16), and Cell Death-Inducing DFFA-Like Effector A (CIDEA) [96–98]. The potential of increased energy expenditure by promoting browning in obesity treatment has been previously reviewed [99]. However, although PPARγ agonist administration induced browning of white adipocytes, PPARγ overexpression had no such effect [93]. Previous studies have shown that administration of dual agonists, compounds activating two targets simultaneously, surpass effects that are reached by conventional agonists [100]. Interestingly, in vivo simultaneous activation of PPARα and PPARγ through dual agonists synergistically induced browning of white adipocytes [101]. Moreover, combinatorial PPARα and γ activation reduced body weight and ameliorated insulin resistance in diet induced obesity, mainly through FGF21 signaling. Although PPARα is the key regulator of FGF21 expression [12], its effects on browning rely on pharmacological PPARγ activation [101].

Not only white adipocyte metabolism and the white-to-brown transition of adipocytes are regulated by PPARγ, but also BAT relies on normal PPARγ function. In BAT, PPARγ is essential for adipogenesis, adipocyte differentiation, survival, and functionality [90, 102–106]. Similar to WAT, PPARγ ablation in BAT inhibited adipocyte formation [90, 102]. In addition, mature brown adipocytes lost their ability to induce non-shivering thermogenesis as PPARγ directly regulated the key thermogenic proteins UCP1 and PRDM16 [104, 107]. Accordingly, chronic treatment of mice with the PPARγ agonist rosiglitazone increased UCP1 levels in brown adipocytes, and thereby thermogenesis [103]. Interestingly, PGC1α, a PPARγ target gene itself [108], directly interacted with PPARγ to enhance UCP1 gene expression [109]. Conversely, mice lacking PGC1α failed to induce thermogenesis in response to cold exposure [110]. The interaction between PPARγ and PGC1α is highly tissue- and target gene-specific. For example, PGC1α was differentially expressed between BAT and WAT [109], suggesting a BAT-specific function. Moreover, PPARγ-controlled FABP4 expression was PGC1α independent [109], indicating that PCG1α selectively facilitated PPARγ mediated thermogenesis in BAT. Apart from UCP1 expression, rosiglitazone administration upregulated triacylglyceride (TAG) synthesis [103], underlining the importance of PPARγ in BAT, as it regulates expression of key proteins but also the formation of substrates for non-shivering thermogenesis.

Taken together, PPARγ regulates many aspects of white and brown adipose tissue metabolism, which reveals PPARγ as highly promising target for metabolism associated abnormalities. Browning of adipocytes especially, but also increased combusting of energy through BAT, represent two intriguing possibilities to counteract obesity and its related morbidities. To date, the investigation of novel drugs for the treatment of obesity in humans by the induction of browning of white adipocytes has proven difficult.

## 4.4 Muscle

Skeletal muscle is the largest metabolically active organ in the human body. It is the major site of insulin dependent glucose uptake, glycogen storage, and fatty acid oxidation. Under metabolic disorders such as obesity and diabetes, severe changes occur in the skeletal muscle amongst which the switch from type 1 slow-twitch to type 2 fast-twitch fibers has profound consequences. The transition of the fiber types promotes insulin resistance, further driving the vicious cycle of the metabolic syndrome. Increase of the favorable type 1 slow-twitch muscles will ameliorate the metabolic syndrome by retrieving insulin sensitivity.

### 4.4.1 PPARβ/δ – Regulator of Skeletal Muscle

PPARβ/δ is the key transcription factor in skeletal muscle function and metabolism (Fig. 4.3). In the skeletal muscle PPARβ/δ regulates glucose and fatty acid metabolism [111, 112], myogenesis [113] and the transition from fast glycolytic 2b to slow/fast oxidative 1/2a fibers [114–116]. In mice and humans, PPARβ/δ expression is

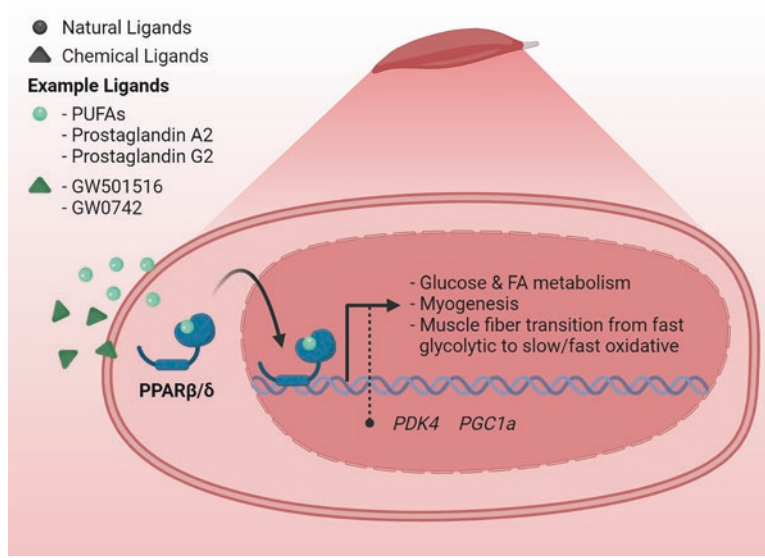


**Fig. 4.3 PPARβ/δ and its main function in muscle metabolism.** In the muscle, PPARβ/δ regulates genes involved in glucose and fatty acid metabolism. Moreover, ligand induced PPARβ/δ activation favours the muscle fiber transition from fast glycolytic to slow/fast oxidative. *PUFA* polyunsaturated fatty acid, *FA* fatty acid, *PDK4* pyruvate dehydrogenase kinase 4, *PGC1α* peroxisome proliferator-activated receptor γ coactivator 1-α

higher in slow/oxidative muscle types in comparison to fast/glycolytic muscles [117, 118] indicating a significant role in muscle type transition. Indeed, during endurance training, which promotes slow/fast oxidative fiber formation, PPARβ/δ expression was elevated [119]. The increase in the number of slow/oxidative muscle fibers upon PPARβ/δ induction resulted from increased muscle progenitor cell abundance, partly through antagonism of myostatin activity, a potent myokine inhibiting muscle growth [113, 120, 121]. Moreover, induction of overexpression of PPARβ/δ improved wheel-running performance, favored the number of slow/fast oxidative 1/2a fibers, and decreased body fat mass in rodents, partly regulated by the PPARβ/δ target gene PGC1α [114, 116, 119]. Interestingly, as observed above PGC1α was also identified as a PPARβ/δ coactivator [109], leading to a feed-forward loop which ensures constant PGC1α expression and thereby maintenance of slow/oxidative fibers [122, 123]. Accordingly, muscle specific overexpression of PGC1α phenocopies PPARβ/δ overexpression suggesting that both PGC1α and PPARβ/δ facilitate skeletal muscle metabolism and function [123]. Moreover, PPARβ/δ modulates fatty acid metabolism through direct transcriptional control of enzymes involved in lipolysis, lipid uptake, and fatty acid β-oxidation [111, 115]. Regulation of β-oxidation in the muscle by PPARβ/δ is facilitated by its direct target gene pyruvate dehydrogenase kinase 4 (PDK4) [111]. PDK4 inactivates the pyruvate dehydrogenase complex (PDH), which is rate limiting for carbohydrate metabolism, leading to the up-regulation of fatty acid β-oxidation [124]. Accordingly, mice lacking muscle-specific PPARβ/δ suffer from dyslipidemia [115]. In diet-induced and genetic mouse models of obesity, PPARβ/δ agonist administration increased fatty acid β-oxidation and thereby improved dyslipidemia [111]. Moreover, PPARβ/δ agonist treatment improved insulin resistance, elevated proliferation of mitochondria, and reduced lipid droplets in skeletal muscle [111, 116], highlighting the therapeutic potential of PPARβ/δ agonists in the metabolic syndrome. Although agonist-activated PPARβ/δ was shown to oppose T2DM and obesity progression, and mimiced endurance training, none of the PPARβ/δ agonists has reached human application yet. This is largely because, apart from the overall positive effects on skeletal muscle metabolism, PPARβ/δ agonist administration was linked to liver fibrosis and hepatic carcinoma [125, 126]. In a recent study, novel and highly muscle-specific PPARβ/δ agonists were synthesized [127], yet remain to be tested for efficiency and side effects. The devel-

opment of tissue-specific PPARβ/δ agonists is crucial in order to bypass the severe side effects in other tissues which limit their potential to improve skeletal muscle function.

## 4.5 Pancreas

Pancreatic β-cells are the main regulators of glucose homeostasis as they secrete insulin in response to glucose, enabling glucose uptake into peripheral tissues. Chronic elevation of blood glucose levels results in β-cell hypertrophy, exhaustion, and dysfunction. Hallmarks of β-cell dysfunction are loss of identity, apoptosis, and insufficient insulin secretion, promoting the progression of T2DM. Counteracting β-cell dysfunction by nuclear receptor manipulation might prevent progression of diabetes.

### 4.5.1 The NR4A Family of Orphan Nuclear Receptors as Regulators of β-Cell Physiology

The NR4A family of orphan nuclear receptors comprises of three members: nuclear receptor 4 A1 (NR4A1), NR4A2, and NR4A3. All three were identified as important regulators of apoptosis, inflammation, and metabolism. While no function in β-cells for NR4A2 was reported thus far, the NR4A members NR4A1 and NR4A3 have gained substantial interest in pancreatic β-cell research and their roles are summarized in Fig. 4.4. NR4A1 expression was induced by glucose and fatty acids in β-cells [128, 129], indicating a significant role of NR4A1 in β-cell function and metabolism. Indeed, the NR4A1 promoter was hypomethylated in pancreatic islets from T2DM patients and mouse models of T2DM and in turn, induction of NR4A1 expression decreased blood glucose levels [130]. Moreover, NR4A1 deletion in insulin-secreting INS1 832/13 cells inhibited glucose stimulated insulin secretion through impaired mitochondrial respiration and tricarboxylic acid cycle [131, 132]. Additionally, NR4A1 was characterized as a direct NK homeobox 6.1 (NKX6.1) target and thereby induced β-cell proliferation in rat pancreatic islets through up-regulation of cell cycle activating genes [133]. Surprisingly, in MIN6 cells – a murine insulinoma β-cell line capable of insulin secretion in response to glucose stimulation [134] – fatty acid induced NR4A1 expression impaired insulin biosynthesis and insulin secretion through direct protein-protein interaction with forkhead box protein O1 (FOXO1) and down-regulation of pancreatic and duodenal homeobox 1 (PDX-1), MAF BZIP transcription factor A (MAFA), and neurogenic differentiation 1 (NEUROD1), essential transcription factors regulating β-cell identity and function [135]. Apart from insulin secretion, NR4A1 directly regulates endoplasmic reticulum (ER) stress induced apoptosis. ER stress, a result of sustained hyperglycemia and dyslipidemia, is a driver for T2DM progression by inducing apoptosis in pancreatic β-cells [136]. Interestingly, NR4A1 expression positively correlated with the induction of ER stress in vitro and ex vivo, while overexpression of NR4A1 ameliorated ER stress induced apoptosis [136, 137]. NR4A1 was identified as mitogen-activated protein kinase phosphatase 7 (MKP7) transcription factor, which counteracted c-Jun N-terminal kinase (JNK) activity and thereby apoptosis by dephosphorylation of JNK [138]. The lack of suitable and specific NR4A1 ligands has hampered detailed research on NR4A1 function in β-cells. Although cytosporone B (Csn-B) was identified as one of the first naturally occurring agonists for NR4A1, its effects on β-cells remain to be investigated [139]. Systemically, Csn-B administration resulted in increased blood glucose levels partly induced by upregulation of gluconeogenic genes in the liver. Additionally, Csn-B induced apoptosis in tumor cells to inhibit xenograft tumor growth [139], highlighting its promising properties to treat hypoglycemia and cancer.

Similar to NR4A1, findings on NR4A3 function in β-cells are contradictory. Initially, NR4A3 was proposed as novel candidate gene for β-cell function, as common genetic variations within the NR4A3 locus were associated with improved insulin secretion [140]. Glucose, fatty acids, and pro-inflammatory cytokines promote NR4A3

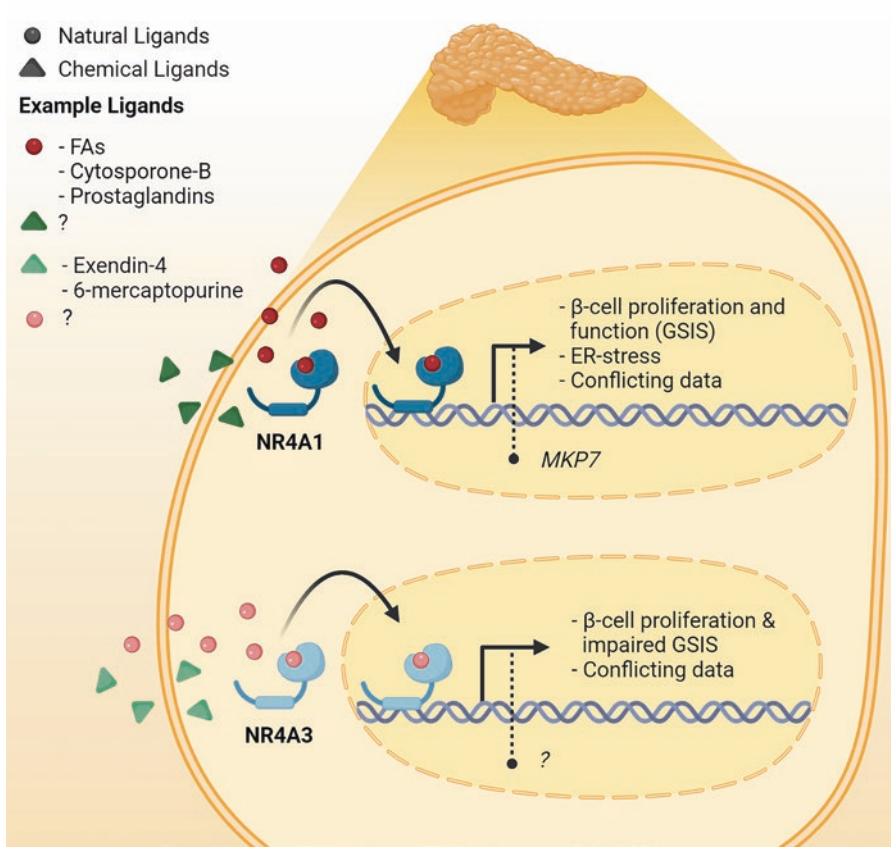


**Fig. 4.4 The orphan nuclear receptors NR4A1 and NR4A3 and their function in β-cells.** Ligands, main mode of action, and key target genes of NR4A1 and NR4A3 in the pancreatic β-cells. For both nuclear receptors, studies are contradictory. (**a**) NR4A1 expression promotes β-cell proliferation and ameliorates ER stress induced apoptosis through MKP7. However, NR4A1 expression was also associated with impaired β-cell functionality. (**b**) NR4A3 was described as positive regulator of β-cell proliferation. However, NR4A3 expression was linked to impaired β-cell function. The underlying conflicting results might be explained by the different models used in the respective studies. *FA* fatty acid, *MKP7* Mitogen-activated protein kinase phosphatase 7

gene expression [141, 142]. Accordingly, NR4A3 expression was elevated in human islets from T2DM patients in comparison to healthy controls, while global NR4A3 deletion in mice resulted in increased β-cell mass, enhanced β-cell proliferation, and improved glucose tolerance [141]. Additionally, in vitro NR4A3 overexpression negatively correlated with insulin gene expression and secretion [142], suggesting NR4A3 activity impaired β-cell function (Fig. 4.4). Unexpectedly, NKX6.1 was also characterized as a direct regulator of NR4A3 expression, and NR4A3 overexpression promoted β-cell proliferation [133]. Various compounds directly regulate NR4A3 activity. 6-Mercaptopurine was identified as specific NR4A3 agonist in skeletal muscle [143, 144]. Moreover, NR4A3 expression was induced by β-adrenergic receptor agonists, indicating a role in lipid metabolism [145]. Further, exendin-4 was shown to attenuate NR4A3 expression in vascular smooth muscle cells [146]. However, the effects and functionality on β-cells remain to be shown.

In summary, current data support a direct regulatory function of the orphan nuclear receptors NR4A1 and NR4A3 in β-cell functionality and metabolism. The conflicting results on NR4A1 and NR4A3 regulated insulin gene expression and secretion may be explained by the different models used in the respective studies. The conduction of in vivo studies with β-cell specific

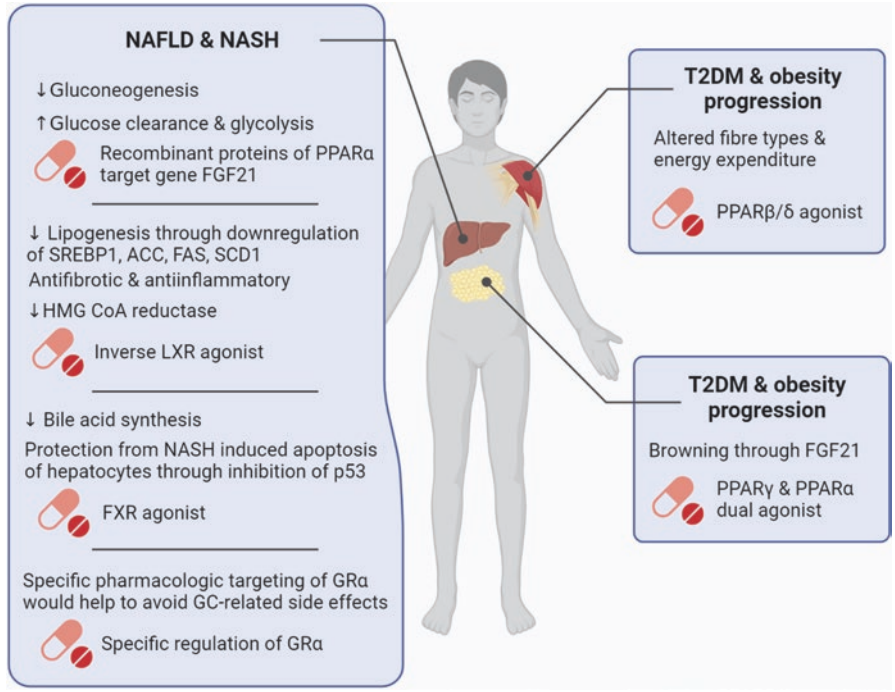


**Fig. 4.5 Potential treatment strategies in metabolic diseases.** Exemplary treatment strategies for metabolic diseases by pharmacologically targeting nuclear receptors. (**a**) NAFLD & NASH treatment: Recombinant FGF21 proteins downregulate hepatic gluconeogenesis and promote glucose clearance and glycolysis. Inverse LXR agonists reduce lipogenesis and reduce plasma cholesterol levels though inhibition of HMG CoA reductase. FXR agonists reduce bile acid synthesis and thereby protect from NASH induced apoptosis in hepatocytes. Specific GRα manipulation would avoid glucocorticoid induced side effects, which are likely induced by GRβ. (**b**) T2DM and obesity progression: PPARβ/δ activity alters fiber types and increases energy expenditure. A dual PPARα and PPARγ agonist induces browning of white adipocytes and thereby increases energy expenditure. *FGF21* fibroblast growth factor 21, *SREBP* sterol regulatory element-binding transcription factor 1, *ACC* acetyl-CoA carboxylase, *FAS* fatty acid synthase, *SCD1* stearoyl-CoA desaturase

NR4A manipulation will help to further understand the function of NR4A1 and NR4A3 in β-cells. Additionally, the continuous search for novel specific agonists is essential for clinical applications such as in the treatment of β-cell dysfunction in T2DM.

## 4.6 Conclusion

Nuclear receptors are key regulators of metabolism and their function is indispensable for metabolic health. Together with co-factors and other co-regulators, they govern a wide range of tissue- and context-specific functions influencing lipid and glucose metabolism. As a result, manipulation and therapeutic targeting of nuclear receptor function has been intensively studied and continues to produce novel and promising drug candidates for metabolic diseases including T2DM, NAFLD, and NASH (Fig. 4.5).

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