

# Metabolic Regulation by Nuclear Receptors

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**Abstract** Nuclear receptors (NRs) are a large family of ligand-dependent transcriptional regulators that control development, reproduction, metabolism, and inflammation. Cognate ligands include fatty acids, bile acids, steroids, vitamins A and D, and thyroid hormone, which enable NRs to sense lipophilic nutrients levels and control their respective flux and metabolism. While major metabolic outputs of some individual receptors are well studied, an integrated understanding of their contributions to systemic metabolic homeostasis is just starting to be revealed. In this chapter, we summarize recent advances in NR signaling in metabolism, with a focus on the emerging paradigm that positions NRs as hubs that translate environmental signals of a particular physiological state into daily metabolic rhythms. As NRs are a proven class of therapeutic targets, these novel findings provide insight into therapeutics for the metabolic syndrome.

**Keywords** Nuclear receptors • Energy homeostasis • Metabolite signaling • Microbiome • FGFs • Metabolic diseases

## Introduction

The human body maintains relatively stable levels of key energy substrates through metabolic flexibility [1]. After a meal, elevated blood glucose triggers insulin release to facilitate glucose uptake in the liver and muscles while simultaneously suppressing free fatty acid release from adipose tissue. Between meals, a complex

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counter-regulatory hormonal network maintains a steady blood glucose level via hepatic glycogen breakdown and gluconeogenesis while concurrently decreasing circulating insulin levels to allow adipose tissue lipolysis to release free fatty acids as the major source of energy. Hence, metabolic flexibility can also be described as the ability to switch between carbohydrates and lipids as the predominant source of energy [1].

While metabolic flexibility undoubtedly provided a survival advantage during our early hunter–gatherer times, in combination with excess nutrients it is now driving the human body to a crisis point. Obesity is now a worldwide epidemic and is often accompanied by pathologies such as type 2 diabetes, hepatosteatosis, and cardiovascular diseases. The excessive accumulation of lipids in tissues brought about by modern day excess nutrient uptake, a condition termed as lipotoxicity [2], often results in insulin resistance and hyperglycemia, and leads to metabolic inflexibility of the body.

At the cellular level, metabolic flexibility utilizes energy sensors, among which are nuclear receptors (NRs), that either activate or inhibit specific metabolic pathways. NRs in humans are comprised of a family of 48 ligand-dependent transcription factors with conserved molecular architecture that includes a DNA-binding domain and a ligand-binding domain [3]. Ligands for NRs consist of a diverse array of small lipophilic molecules [3], which, upon binding to their cognate NR, recruit enzymatic cofactors to modulate their target gene expression and, thereby, physiological output. A small subset of NRs have been identified as major players in the maintenance of metabolic flexibility via their ability to sense key lipophilic dietary nutrients and regulate a complex network of genes to control the metabolic flux of these nutrients.

Intensive research over the past two decades has established the fundamental mode of action of a subset of individual receptors (Table 1), including the peroxisome proliferator-activated receptors (PPARs), farnesoid X receptor (FXR), and liver X receptors (LXR<sub>s</sub>). We will summarize the recent progress in elucidating how these receptors coordinate metabolic homeostasis in response to dietary intake and environmental stressors.

## **NR Endogenous Ligands Are Dietary Sensors**

The generation and degradation of prototypical endogenous NR ligands through enzymatic modifications, such as those catalyzed by cytochrome P450 (CYP) enzymes [3, 9], allows for integration with NR-independent regulatory pathways. For example, regulation of FOXO1 activity by hepatic insulin signaling determines the expression level of CYP7A1, the rate-limiting P450 enzyme in the synthesis of bile acids, the endogenous ligands for FXR [10].

In the case of the PPARs, each binds fatty acids with relatively low affinity and regulates metabolic homeostasis through canonical direct repeat 1 (DR1) elements within promoters and enhancers of target genes. Specificity is achieved at the level

**Table 1** Nutrient-sensing nuclear receptors

	Ligand	Expression	Function
PPAR $\alpha$	Short-chain fatty acids	Liver	PPAR $\alpha$ was first identified as the target of the lipid-lowering drug phenofibrate. PPAR $\alpha$ is a master regulator of the adaptive fasting response in the liver. In the fasted state, elevated circulating free fatty acids activate hepatic PPAR $\alpha$ , whose targets include rate-limiting enzymes in fatty acid oxidation and ketogenesis [4]. PPAR $\alpha$ knockout mice die upon prolonged fasting with excessive hepatic fatty acid accumulation
PPAR $\gamma$	15-deoxy-Delta-12,14-prostaglandin J2 and thiazolidinedione antidiabetic drugs	Adipose tissue	PPAR $\gamma$ is the master regulator of adipogenesis and lipogenesis, and is required for both white and brown adipose tissue formation. Postprandial increase in fatty acids activates adipose PPAR $\gamma$ to facilitate fat storage and production of adipokines (leptin, adiponectin, resistin, etc.), which are important regulators of whole-body insulin sensitivity [4, 5]
PPAR $\delta$	Long-chain fatty acids	Ubiquitously expressed	PPAR $\delta$ activation enhances fatty acid oxidation and mitochondrial respiration. PPAR $\delta$ activation in white adipose tissue promotes its conversion to brown fat, whereas in the muscle, it increases oxidative type I fiber formation. In the liver, PPAR $\delta$ controls fatty acid synthesis through direct activation of the rate-limiting enzyme <i>Acaca</i> [4, 6]
FXR	Bile acids	Liver, kidney, and intestine	FXR regulates bile acid homeostasis by promoting bile acid reabsorption in the gut and suppressing de novo bile acid synthesis in the liver [7, 8]
LXR	Oxysterols	LXR $\alpha$ : liver, adipose tissue, and macrophages; LXR $\beta$ : ubiquitously expressed	LXRs promote cholesterol efflux in the liver via 3 mechanisms: (1) suppression of cholesterol uptake from LDL recycling; (2) production of VLDL for export; (3) conversion of cholesterol to bile acids for excretion. LXRs exert an opposing effect to FXR on bile acid metabolism [8]

*Acaca* acetyl-coA carboxylase 1, *FXR* farnesoid X receptor, *LDL* low-density lipoprotein, *LXR* liver X receptor, *PPAR* peroxisome proliferator-activated receptor, *VLDL* very low-density lipoprotein

of the ligand, enabling the body to enact different physiological responses using common elements within the genome. Long-chain fatty acids preferentially activate PPAR $\delta$  to stimulate fatty acid oxidation in skeletal muscle. In contrast, PPAR $\alpha$  activation by short-chain fatty acids switches on a feed-forward mechanism in the liver to promote fuel oxidation, thereby preventing the intracellular accumulation of fatty acids and consequent lipotoxicity. Thus, the coordinated actions of these PPARs protect against lipotoxicity through the regulation of different metabolic target tissues in response to the uptake of fatty acids.

## Gut and Gut Microbiota

There is growing evidence that the modern lifestyle, most notably the high-fat/high-sugar “Western” diet, has altered the genetic composition and metabolic activity of our resident microorganisms. The microbiome communicates with NRs through its ability to modify dietary nutrients to generate specific NR ligands. An early example is oleoylethanolamide (OEA), a high-affinity PPAR $\alpha$  ligand generated in enterocytes from oleic acid [11]. OEA-induced activation of intestinal PPAR $\alpha$  enhances fat absorption through induction of the target gene, CD36, and promotes satiety through a secondary signaling cascade in the brain [12].

More recently, an enhanced bile acid flux was observed throughout the intestinal tract of germ-free mice [13], suggestive of dysregulated FXR activity. While it was known that intestinal microbiota metabolize primary bile acids to increase their hydrophobicity and chemical diversity [13, 14], it was not known to what extent the microbiota influence FXR activity. The serum bile acid composition of the germ-free mice revealed elevated levels of tauro-conjugated alpha- and beta-muricholic acids (T $\alpha$ / $\beta$ MCA), known FXR antagonists [13, 15], which result in a loss of feedback inhibition of bile acid synthesis. Importantly, this study demonstrates that endogenous FXR antagonists are default products of the canonical bile acid synthesis pathway, raising interesting questions about the co-evolution of crucial NR-dependent metabolic pathways and the intestinal microbiome.

An added biological complexity to this system is that reciprocally, bile acids can influence the composition of the intestinal microbiome. A diet high in saturated fatty acids increases tauro-conjugated cholic acid concentrations to promote the growth of sulfate-consuming bacteria, increasing the susceptibility of mice to colitis [16]. This dynamic relationship between bile acids and microbiota is still not well understood, making it difficult to predict the metabolic outcome when deregulation occurs. For example, while FXR null mice are more susceptible to metabolic disorders [17–19], intestinal-specific FXR knockout mice are protected [15]. Clinically, the importance of this pathway was demonstrated in a recent study, which showed that the metabolic benefits of vertical sleeve gastrectomy were mediated by the gut microbiota and FXR signaling in the intestine [20].

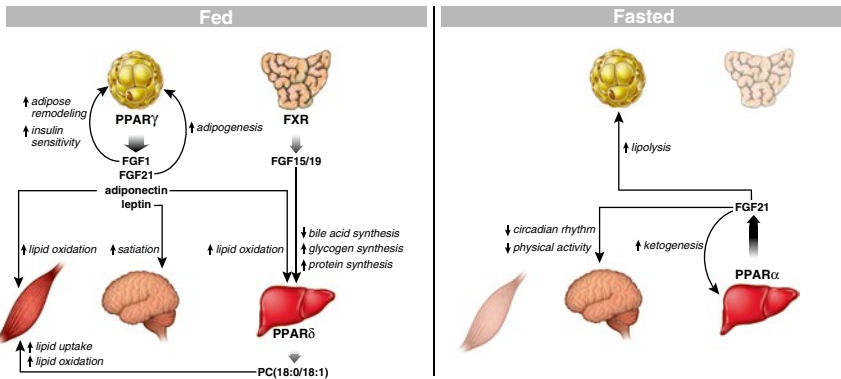
## De Novo Lipogenesis

In contrast to the relatively well-understood metabolic actions of dietary lipids, the effects of the largely monounsaturated fatty acids generated in the liver through de novo lipogenesis are now being explored [21]. Utilizing genetic mouse models to disrupt hepatic de novo lipogenesis, researchers have demonstrated a broad spectrum of metabolic changes on fat-free diets [22, 23]. Loss of fatty acid synthase (FAS)—a rate-limiting enzyme in de novo lipogenesis—in the liver leads to the development of a fatty liver upon fasting, similar to a PPAR $\alpha$  knockout phenotype [24, 25]. Importantly, this fatty liver phenotype can be rescued with a PPAR $\alpha$  synthetic ligand, implicating de novo fatty acid synthesis in the generation of endogenous PPAR $\alpha$  ligands. Furthermore, the authors identified a phosphocholine (16:0/18:1-GPC) as an endogenous ligand for PPAR $\alpha$  [24]. In adipose tissue, lipogenesis has been implicated in producing PPAR $\gamma$  endogenous ligands [26], such as 1-O-octadecenyl-2-palmitoyl-3-glycerophosphocholine (18:1e/16:0-GPC) [27].

Direct biochemical approaches have identified endogenous ligands for PPAR $\alpha$  and PPAR $\gamma$ . How these ligands function in normal physiology when both dietary and de novo synthesized lipids are present is not clear [28]. Although not directly evaluated under diet-induced or genetic obesity, PC(16:0/18:1) is one of two serum phosphocholine species that were observed to have aberrant diurnal rhythmic concentrations [29]. It should be cautioned that “ligands” identified through blocking of an endogenous pathway can be misleading, illustrated by the fact that these phospholipids are weak activators of their respective targets in cell-based reporter systems [24, 27]. However, weak pharmacological activation of PPAR $\alpha$  or PPAR $\gamma$  is beneficial for some metabolic disorders, while, conversely, strong NR activators can carry significant side effects (e.g. rosiglitazone). It was recently shown that a weak PPAR $\gamma$  ligand could achieve similar therapeutic responses to rosiglitazone with limited side effects [30, 31]. Exploring the therapeutic values of these endogenous ligands will be an exciting next step.

## Integrative Physiology—Nuclear Receptor-Mediated Crosstalk

Metabolic flexibility results from cohesive actions of major metabolic organs in response to nutrient flux. It is a collective consequence of localized activation of cellular nutrient-sensing pathways and systemic hormonal actions. Whereas hormones can be released from specialized endocrine organs that directly sense nutrients, they can also be produced from metabolic organs to amplify or propagate local nutrient cues. One example of the latter is the adipose PPAR $\gamma$ -mediated production of adipokines such as leptin and adiponectin [5]. In the postprandial setting,



**Fig. 1** Integrative physiology through nuclear receptor (NR)-mediated crosstalk. Nutrient-sensing NRs amplify or propagate nutrient signals through local and long-range hormone actions. In the fed state, intestinal farnesoid X receptor (*FXR*) activation resulting from bile acid release produces fibroblast growth factor (*FGF*) 15/19. FGF15/19 limits hepatic bile acid synthesis and promotes glycogen and protein synthesis to store nutrients. Postprandial carbohydrate and lipid influx activate a hepatic peroxisome proliferator-activated receptor (*PPAR*) $\delta$ -controlled lipid synthesis program. The phosphocholine PC(18:0/18:1) is secreted as a long-range hormone to promote muscle fat utilization. Feeding activates adipose tissue *PPAR* $\gamma$ , which, in turn, controls the release of multiple adipokines. Locally, FGF21 amplifies *PPAR* $\gamma$  signaling and promotes further adipogenesis. FGF1 is another paracrine signal that is essential for healthy adipose tissue remodeling and for maintaining whole-body insulin sensitivity. Systemically, adiponectin enhances lipid oxidation in muscle and liver, whereas leptin increases satiety by acting on the central nervous system. During fasting, hepatic *PPAR* $\alpha$  activation secretes FGF21, whose pleiotropic effects, including elevated adipose tissue lipolysis and hepatic ketogenesis, are important for adaptive fasting response. In addition, FGF21 interferes with the circadian clock in the brain and modulates physical activities

*PPAR* $\gamma$  induces leptin production to enhance satiety in the central nervous system (CNS), as well as the release of adiponectin to promote fatty acid oxidation in the liver. The dual regulation of central and peripheral responses creates the needed coordination to maintain metabolic balance.

Given the critical roles of the aforementioned NRs in cellular nutrient sensing, it is perhaps not surprising that some of these NRs have been shown to produce hormone-like molecules (Fig. 1). To date, two classes of secreted molecules have been prominently linked with these NRs: the fibroblast growth factors (FGFs) and lipids.

## Fibroblast Growth Factors

Screening for genes activated by nutrient-sensing NRs identified several FGFs as highly induced [32, 33] (Table 2). There are 22 FGFs (FGF1–FGF23) in the human genome (FGF15 is the mouse ortholog of human FGF19 [34]) that are classified as classic or endocrine FGFs. Most classic FGFs are secreted, heparan sulfate-binding

**Table 2** Nutrient-regulated fibroblast growth factors (FGFs)

Nuclear receptor	FGF	Physiological state
FXR	FGF15/19	Fed
PPAR $\alpha$	FGF21	Fasted
PPAR $\gamma$	FGF21	Fed
PPAR $\gamma$	FGF1	Fed

*FXR* farnesoid X receptor, *PPAR* peroxisome proliferator-activated receptor

proteins that interact locally with fibroblast growth factor receptors (FGFRs) as autocrine/paracrine factors to modulate cell growth, angiogenesis and wound healing [34]. In contrast, the endocrine FGFs (FGF15/19, FGF21, and FGF23) bind heparan sulfate poorly, thereby escaping the extracellular matrix to circulate in the blood. Furthermore, the endocrine FGFs require  $\alpha$ - and  $\beta$ -klotho co-receptors for signal transduction.

After consuming a meal, the liver takes up 25–35 % of dietary carbohydrates [35]. This effect cannot be replicated by either systemic hyperglycemia or hyperinsulinemia, suggesting that crosstalk between the gastrointestinal tract and liver is critical for hepatic glucose utilization. More importantly, feeding-induced hepatic glycogen synthesis remains functional in a genetic model that lacks insulin signaling in the liver [36, 37], raising the possibility of a parallel pathway to control postprandial hepatic metabolic reprogramming. Postprandial bile acid release and subsequent reabsorption are integral responses to feeding. The reabsorption of bile acids in the intestine leads to the activation of intestinal FXR and the subsequent secretion of FGF15/19, a direct target of FXR. Originally found to suppress hepatic de novo synthesis of bile acids [32], FGF15/19 has recently been found to promote hepatic glycogen synthesis and protein synthesis by activating the Ras–extracellular signal-related kinase (ERK) pathway, a parallel pathway to the insulin-activated PI3K–AKT pathway [38]. These findings implicate FGF15/19 in the coordination of intestinal feeding responses with hepatic metabolic changes.

In the fasted state, the coordinated activation of hepatic fatty acid oxidation and white adipose tissue lipolysis constitutes a major axis of energy substrate switch from carbohydrate to lipids. FGF21, a hepatic PPAR $\alpha$  target gene, was found to play important roles in liver-adipose crosstalk during fasting [33, 39]. As serum levels of FGF21 correlate closely with hepatic FGF21 expression [40], the liver is thought to be the major source of circulating FGF21. FGF21 promotes free fatty acid release from white adipose tissue by activating several lipases, thereby providing substrates for hepatic fatty acid oxidation and ketogenesis. In addition, FGF21 enhances hepatic ketogenesis through increasing the protein levels of rate-limiting enzymes in ketogenesis.

However, the adaptive fasting response, especially after prolonged fasting, requires the coordinated actions of all major organs to enhance survival. Recently, FGF21 was found to suppress physical activity, alter circadian behavior, and reduce female fertility [41, 42]—actions known to be involved in the physiological response to prolonged fasting. Moreover, these adaptive responses were attributed to FGF21 activity in the suprachiasmatic nucleus (SCN) region of the brain.

Interestingly, pharmacological administration of FGF21 elicits pleiotropic effects beyond the changes seen in the adaptive fasting response [43, 44], suggesting additional roles of FGF21 in other physiological settings. Indeed, FGF21 was found to be a target of PPAR $\gamma$  in adipose tissue, where its paracrine actions potentiate PPAR $\gamma$  activation in the postprandial state [40]. Notably, the effects of FGF21 on glucose homeostasis and hepatic lipid metabolism were shown to be dependent on adiponectin, a PPAR $\gamma$ -induced adipokine [44].

In addition to liver and white adipose tissue, FGF21 is produced in brown fat [45] and skeletal muscle [46] in response to specific stimuli, suggesting that FGF21 coordinates the tissue-specific responses of the major metabolic organs.

The expressions of FGF15/19 and FGF21 are exquisitely dynamic during fasting and feeding cycles [32, 33, 40, 47]. The nutrient-responsive nature of FGF21 and FGF15 expression opens a new chapter for their respective roles in metabolism. In contrast, the prototypic FGF1 and FGF2 [34] are ubiquitously expressed [48], with established roles in wound healing and brain development [34]. Whereas FGF2 knockout mice have mild brain development and wound healing defects, FGF1 knockout mice are phenotypically normal [49]. In search of additional FGFs that may act as nutrient-controlled hormones, FGF1 was found to be highly induced in white adipose tissue upon feeding of a high-fat diet [50]. Conversely, FGF1 knockout (FGF1KO) mice developed marked adipose tissue fibrosis, impaired glucose homeostasis, and insulin insensitivity when fed a high-fat diet. Furthermore, upon withdrawal of the high-fat diet, FGF1KO mice developed pronounced fat necrosis. Given that adipose tissue expansion accompanied by increased vascularization is required to maintain insulin sensitivity under conditions of nutrient surplus [51], the poor white adipose tissue vascularization observed in FGF1 knockout mice may be responsible for their severe insulin-resistant phenotype on a high-fat diet. Interestingly, FGF1 is shown to be directly regulated by PPAR $\gamma$ , and PPAR $\gamma$  and its target genes are increased in FGF1 knockout mice [50]. Therefore, FGF1 appears to be an essential output for PPAR $\gamma$ -mediated insulin sensitization. Distinct from FGF21-mediated amplification of PPAR $\gamma$ -mediated adipogenesis and adipokine production [40], FGF1 does not promote adipogenesis in 3 T3-L1 cells [52]. These properties raise the intriguing possibility of recombinant FGF1 (rFGF1) as an antidiabetic drug that may minimize the side effects associated with the thiazolidinedione class of PPAR $\gamma$  agonists. Indeed, rFGF1 injection markedly improves insulin sensitivity in genetic and diet-induced obesity models [53]. These effects are insulin dependent, suggesting a role as an insulin sensitizer, and require adipose FGFR1 expression, as rFGF1 fails to lower blood glucose in FGFR1 adipose-specific knockout mice. Interestingly, rFGF1 treatment does not alter adipose tissue vasculature, indicating differences between pharmacological administration and genetic studies. Importantly, an N-terminally truncated FGF1 analog with markedly reduced mitogenic activity was similarly able to normalize blood glucose levels in



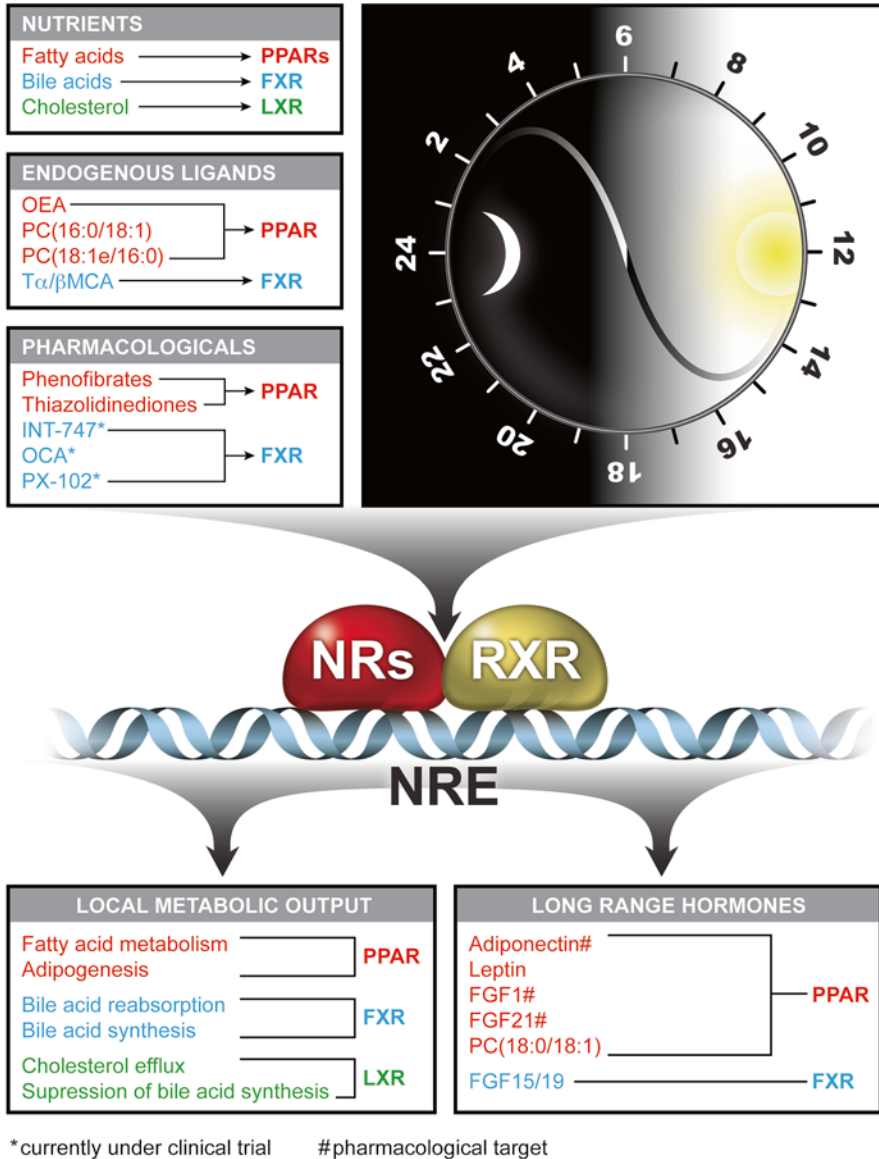
diabetic mice [53]. The ability to dissociate the mitogenic and glucose-lowering activities of FGF1 suggests that these different effects may be receptor specific. Nevertheless, these results demonstrate that FGF1 is a critical mediator of nutrient responsiveness in adipose tissue and has significant therapeutic potential.

## Lipids

De novo lipogenesis has emerged as a novel pathway that produces lipid signaling molecules, including NR ligands. It was found that activation of PPAR $\delta$  in the liver enhanced hepatic de novo lipogenesis but paradoxically reduced serum lipid concentrations [6, 29]. The reduction of serum lipids was also correlated with increased fatty acid uptake and oxidation in the skeletal muscle. Through unbiased metabolomics profiling, phosphocholine PC(18:0/18:1) was identified as a signaling molecule that facilitates postprandial crosstalk between the liver and muscle to promote fatty acid utilization. Furthermore, the effects of PC(18:0/18:1) are mediated by another NR, PPAR $\alpha$ , in the muscle, underlying a new model of tissue crosstalk through NRs.

## Concluding Remarks

In 1995, 10 years after the cloning of the first NR, the glucocorticoid receptor, the challenge of the field was proposed: "...to elucidate the contributions of these individual systems to the integrated and complex processes associated with the multihormonal nature of metabolic regulation..." [54] This review summarizes our current understandings toward this challenge. An immediate implication of our expanded knowledge of endogenous ligands and downstream hormonal signals is to explore their potential as novel therapeutics. Indeed, several compounds are in clinical trials for metabolic syndrome. In addition, these recent advances have highlighted the role of nutrient-sensing NRs in coordinating metabolic homeostasis. Through receptor activation, environmental cues are transduced as local metabolic outputs and long-range hormonal actions (Fig. 2). In a reductionist's perspective, these receptors may be important on-off switches for specific physiological states [55]. While wholesale, prolonged activation of any of these receptors may not be desirable, the use of high-affinity synthetic ligands offers a window to tease out beneficial downstream targets, especially in light of the identification of several hormone-like molecules that are good therapeutic candidates. With readily available synthetic ligands and mouse genetic models, it is possible that these receptors will become platforms for drug discovery.



**Fig. 2** Nuclear receptors (*NRs*) as hubs to transduce environmental signals into daily metabolic rhythms. Originally identified as sensors for lipophilic nutrients to control their respective ligand metabolism, emerging evidence points to an integrative nature of the regulation and action of the peroxisome proliferator-activated receptor (*PPAR*), farnesoid X receptor (*FXR*), and liver X receptor (*LXR*) families of *NRs*. In addition to nutrients, their activities are fine-tuned by endogenous ligands and the circadian clock. Activation of these *NRs* not only controls key cellular metabolic programs but also produces hormones that further connect metabolic tissues for a cohesive response to nutrient flux. Given the central roles of *NRs* in nutrient signaling, several pharmacological agents have been developed or are in development for metabolic diseases. Additionally, the *NR*-controlled hormones represent yet another emerging venue for therapeutics

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