

# International Union of Pharmacology. LXII. The NR1H and NR1I Receptors: Constitutive Androstane Receptor, Pregnane X Receptor, Farnesoid X Receptor $\alpha$ , Farnesoid X Receptor $\beta$ , Liver X Receptor $\alpha$ , Liver X Receptor $\beta$ , and Vitamin D Receptor

DAVID D. MOORE, SHIGEAKI KATO, WEN XIE, DAVID J. MANGELSDORF, DANIEL R. SCHMIDT, RUI XIAO, AND STEVEN A. KLIEWER

*Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas (D.D.M., R.X.); The Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo, Japan (S.K.); Center for Pharmacogenetics, University of Pittsburgh, Pittsburgh, Pennsylvania (W.X.); Howard Hughes Medical Institute, Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, Texas (D.J.M., D.R.S.); and Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, Texas (D.J.M., D.R.S., S.A.K.)*

**Abstract**—The nuclear receptors of the NR1H and NR1I subgroups include the constitutive androstane receptor, pregnane X receptor, farnesoid X receptors, liver X receptors, and vitamin D receptor. The newly emerging functions of these related receptors are un-

der the control of metabolic pathways, including metabolism of xenobiotics, bile acids, cholesterol, and calcium. This review summarizes results of structural, pharmacologic, and genetic studies of these receptors.

## Introduction

The 48 members of the nuclear hormone receptor superfamily can be divided into approximately equal-sized groups of conventional receptors with known ligands and orphan receptors that lack them (Willson and Moore, 2002). The conventional receptors can be further subdivided into comparably sized subgroups of classic receptors, whose ligands were well known before their cDNAs were cloned, and new receptors that are often termed “adopted orphans.” The majority of the new receptors are in the NR1H<sup>1</sup> and NR1I subfamilies.

Address correspondence to: Dr. David D. Moore, Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX 77030. E-mail: moore@bcm.tmc.edu

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<sup>1</sup> Abbreviations: NR, nuclear receptor; RXR, retinoid X receptor; PPAR, peroxisome proliferator-activated receptor; LXR, liver X receptor; FXR, farnesoid X receptor; PXR, pregnane X receptor; CAR, constitutive androstane receptor; VDR, vitamin D receptor; SREBP, sterol regulatory element binding protein; SHP, small heterodimer partner; eCH, 24(S),25-epoxycholesterol; AF, activation function; LBD, ligand-binding domain; 1,25(OH)<sub>2</sub>D<sub>3</sub>, 1,25-dihydroxyvitamin D<sub>3</sub>; CITCO, 6-(4-chlorophenyl)imidazo[2,1-b](1,3)thiazole-5-carbaldehyde-O-3,4-dichlorobenzyl)oxime; TCPOBOP, 1,4-bis[2-(3,5-dichloropyridyloxy)]benzene; PCN, pregnenolone-16 $\alpha$ -carbonitrile.

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An intriguing functional theme has developed for the new receptors as a series of RXR heterodimer partners, first the PPARs and then the LXRs (NR1H2 and NR1H3), FXR (NR1H4), PXR (NR1I2), and CAR (NR1I3), have emerged as key regulators of metabolism (Lu et al., 2001; Willson and Moore, 2002; Francis et al., 2003; Shulman and Mangelsdorf, 2005). The PPARs, receptors for fatty acids and the clinically important antidiabetic thiazolidinediones (PPAR $\gamma$ ) and antihyperlipidemic fibrates (PPAR $\alpha$ ), are described elsewhere. A full analysis of the metabolic regulatory roles of the NR1 receptors is outside the scope of this brief review, but the endogenous ligands, primary functions, and sites of expression of the these receptors are summarized in Table 1.

The LXRs are receptors for oxysterols, oxidized cholesterol derivatives that accumulate when cholesterol levels are elevated. LXR $\alpha$  drives cholesterol catabolism in the liver, whereas LXR $\beta$  activates reverse cholesterol transport from the periphery to the liver (Tontonoz and Mangelsdorf, 2003). The bile acid receptor FXR functions as the major regulator of bile acid homeostasis (Lu et al., 2001). This includes direct activation of pathways that repress bile acid biosynthesis and also induce bile acid export from the liver. The xenobiotic receptors CAR and PXR mediate a chemical defense response to potentially toxic foreign compounds and also toxic endogenous compounds by increasing the capacity of the liver and other tissues to metabolize and clear them (Willson and Kliewer, 2002). The vitamin D receptor (VDR) (NR1I1) is the final member of the NR1I subgroup and the only one

TABLE 1  
*Endogenous ligands and primary biologic activities of NR1 subgroup receptors*

NR1H1 is the insect ecdysone receptor.

Receptor	Major Sites of Expression	Endogenous Ligand/Activator	Primary Function
LXR $\alpha$ (NR1H3)	Liver, intestine, fat, lung, macrophage	Oxysterols	Cholesterol homeostasis
LXR $\beta$ (NR1H2)	Broadly expressed	Oxysterols	Cholesterol homeostasis
FXR (NR1H4)	Liver, intestine, kidney	Bile acids	Bile acid homeostasis
VDR (NR1I1)	Intestine, thyroid, kidney	1,25(OH) $_2$ D $_3$	Calcium homeostasis
CAR (NR1I2)	Liver, intestine, choroid plexus	Bile acids, <sup>a</sup> bilirubin <sup>a</sup>	Detoxification
PXR (NR1I3)	Liver, intestine	Bile acids	Detoxification

<sup>a</sup> Elevated levels of bile acids and bilirubin activate CAR indirectly via induction of nuclear translocation, not by functioning directly as agonists.

that had been characterized before the isolation of its cDNA. VDR is primarily associated with calcium homeostasis, not lipid metabolism, but it has recently been identified as an additional bile acid receptor (Makishima et al., 2002).

It should be emphasized that the NR1H and NR1I receptors do not function in isolation but cooperate to coordinate inter-related metabolic responses and also that each has additional important functions. For example, LXR $\alpha$  activation in liver increases not only cholesterol efflux but also triglyceride production by inducing expression of the lipogenic transcription factor SREBP-1c and its target genes (Joseph et al., 2002a). This is consistent with coordinate release of both cholesterol and triglycerides from the liver in lipoproteins. FXR activation regulates cholesterol and triglyceride metabolism in the opposite direction of LXR $\alpha$ , inhibiting both cholesterol conversion to bile acids and triglyceride production (Lu et al., 2001; Claudel et al., 2003). The LXR and FXR responses share some key target genes, such as cholesterol 7 $\alpha$ -hydroxylase, CYP7A1, and SREBP-1c, but are mechanistically quite distinct, with LXR directly activating both, at least in rodents, whereas FXR acts indirectly via induction of the repressor SHP (NR0B2).

Characterization of these new receptors has also revealed novel links among metabolic pathways and between these pathways and other responses. Thus, recent results show that LXR agonists can have unexpected but potentially beneficial effects on glucose metabolism by both down-regulating expression of gluconeogenic target genes in liver and increasing expression of genes involved in glucose uptake in the periphery (Laffitte et al., 2003). More broadly, LXRs (Joseph et al., 2003) have been found to have anti-inflammatory effects. VDR also has a substantial impact on immune function (DeLuca and Cantorna, 2001), although some of the effects may be secondary consequences of alterations in calcium homeostasis (Mathieu et al., 2001).

## Structures

### LXR $\alpha$ and $\beta$

Structures have been solved for LXR $\beta$  bound to the natural agonist 24(S),25-epoxycholesterol (eCH) and the

synthetic agonist T0901317 (Hoerer et al., 2003; Williams et al., 2003). The ligands are retained in the pocket primarily through hydrophobic interactions that orient the A ring of eCH toward helix 1 and the D ring and epoxide tail toward the C-terminal end of helix 10. Distinctive features include a long helix 1 and a relatively large ligand-binding pocket ( $\sim 800 \text{ \AA}^3$ ) compared with the classic steroid hormone receptors. Both eCH and T0901317 stabilize the AF-2 helix in the active configuration through a histidine-tryptophan switch that involves hydrogen bonds between the ligand and the His-435 imidazole ring, which in turn makes an edge to face interaction with the Tyr-487 on the inner surface of the AF-2 helix. LBD structures have been determined for LXR $\alpha$  bound to the synthetic agonist T0901317 and GW3987 and are very similar to that of LXR $\beta$  bound to T0901317 (Svensson et al., 2003). All of the amino acids that line the ligand-binding pocket, including the histidine trigger and the AF-2 tryptophan, are conserved in the two LXR isoforms, so the mechanism of ligand activation seems to be identical.

### FXR $\alpha$

Structures have been solved for FXR $\alpha$  bound to the agonist bile acids 3-deoxychenodeoxycholic acid and 6-ethyl-chenodeoxycholic acid and the synthetic agonist fexaramine (Downes et al., 2003; Mi et al., 2003). Unlike all other steroid-nuclear receptor interactions, the bile acids occupy the  $\sim 700 \text{ \AA}^3$  ligand-binding pocket with their A rings facing the AF-2 helix. The A rings activate a histidine-tryptophan switch that stabilizes the AF-2 helix in the active configuration. Agonist-bound FXR $\alpha$  can interact simultaneously with two LXXLL coactivator motifs: one occupies the primary coactivator binding groove, whereas the other binds to an adjacent site in an antiparallel manner. This second binding site enhances the binding affinity of the coactivator.

### VDR

The first reported VDR structure was for an LBD derivative of the human receptor (VDR $\Delta$ ) in which a 50-amino acid segment between helices 1 and 3 was removed, based on secondary structure prediction programs suggesting that this region was disordered (Rochel et al., 2000). VDR $\Delta$  was crystallized bound to

1,25(OH)<sub>2</sub>D<sub>3</sub>. The ligand-binding pocket is ~700 Å<sup>3</sup> with vitamin D occupying ~60% of this volume. Vitamin D is oriented with its A ring toward the C terminus of helix 5 and its 25-hydroxyl group close to helices 7 and 11. The interaction between vitamin D and VDR involves both hydrophobic and electrostatic interactions. The AF-2 helix is in the agonist conformation and makes two direct Van der Waals contacts with a vitamin D methyl group. The AF-2 helix position is further stabilized by two polar interactions and several hydrophobic contacts. Recently, the structure of the intact zebrafish LBD was solved in complex with 1,25(OH)<sub>2</sub>D<sub>3</sub> and an SRC1 peptide (Ciesielski et al., 2004). The region deleted in VDRΔ was not visible in the electron density map, reflecting its disorder. The binding pocket is identical and makes the same interactions with the ligand seen in the original VDRΔ structure.

### CAR

The structure of the CAR LBD has been solved in complex with the agonists 5β-pregnanedione, CITCO, and TCPOBOP and the inverse agonist androstenol (Shan et al., 2004; Suino et al., 2004; Xu et al., 2004). The structures suggest that the constitutive activity of CAR results from several features including a short helix preceding the AF-2 helix, helix 12, which combines with a salt bridge between C terminus of helix 12 and helix 3 to stabilize the AF-2 helix in the active conformation. The CAR LBD is stabilized further by an extended helix 2 that makes contacts with helix 3. The CAR LBD contains a well-formed ligand-binding pocket of ~600 Å<sup>3</sup> but lacks the sequence motifs that allow the flexible expansion of the PXR pocket. A single residue difference in the C-terminal region of the mouse versus human CAR is proposed to account for the strong species selectivity for some agonists. The CAR-androstenol complex shows that this inverse agonist sterically interferes with the positioning of the AF-2 helix, preventing CAR from interacting with either coactivators or co-repressors.

### PXR

Like VDR, PXR contains an ~60 amino acid region between helix 1 and helix 3. However, in PXR this insert creates an extended five-stranded antiparallel β-sheet and a 13- to 20-amino acid stretch of disordered residues adjacent to the ligand-binding pocket (Watkins et al., 2001). These features generate a ligand-binding pocket with an apo volume of ~1300 Å<sup>3</sup> that can adjust its shape to accommodate ligands of distinct size and structure. Twenty-eight amino acid side chains line the pocket of PXR, of which eight are polar and capable of forming hydrogen bonds with ligands. All ligands examined to date, including the cholesterol-lowering drug SR12813, the antibiotic rifampin, and the St. John's wort constituent hyperforin, form a combination of

hydrophobic and polar interactions with PXR ligand-binding pocket residues (Watkins et al., 2001, 2003a,b; Chrencik et al., 2005).

## Endogenous Ligands

### LXRα and β

The endogenous ligands of the LXRs are a series of oxidized derivatives of cholesterol termed "oxysterols" (Janowski et al., 1996, 1999). Arguments for oxysterols as physiologic agonists for LXRs include their ability to activate the receptors at concentrations comparable with their endogenous levels, the fact that the natural stereoisomers are more active than synthetic variants, and the clear cholesterol-related phenotypes of LXR-null mice. Potential LXR agonists include 24(S),25-epoxycholesterol, which is generated from the cholesterol precursor squalene and is relatively abundant in the liver; 22(R)-hydroxycholesterol, which is a transient intermediate in steroid hormone synthesis; 24(S)-hydroxycholesterol, which is present in the brain; and 27-hydroxycholesterol which is found in macrophages. The two LXR isoforms are very closely related and the endogenous and synthetic agonists characterized to date activate both.

### FXRα

It is now well established that FXRα functions as a bile acid receptor. It can be activated by a very wide range of bile acids, including the primary products cholic acid and chenodeoxycholic acid, and their secondary glycine and taurine conjugates (Makishima et al., 1999; Parks et al., 1999; Wang et al., 1999). The affinities are not equivalent, however, and it seems likely that distinct bile acids may have somewhat different functional effects on FXRα and also the other NRs that they activate, including VDR, PXR, and CAR. Bile acids are produced from cholesterol via a complex series of enzymatic steps that are organized into two main pathways. The initial and rate-limiting step in the classic or neutral pathway is catalyzed by cholesterol 7α-hydroxylase, CYP7A1. Expression of this key enzyme is powerfully repressed when bile acid levels are too high by a nuclear receptor cascade in which the activated FXRα induces expression of the orphan receptor SHP, which in turn shuts off the activity of another orphan receptor, liver receptor homolog-1, which is essential for CYP7A1 promoter activity (Shulman and Mangelsdorf, 2005).

### VDR

In contrast with the recent linkage of the other NR1 receptors with their ligands, the active ligand for the VDR has long been known to be 1,25(OH)<sub>2</sub>D<sub>3</sub>, and both its production and the mechanisms that control its levels are well defined (DeLuca, 1986). 7-Dehydrocholesterol is a vitamin D precursor that is synthesized from cholesterol and is converted into vitamin D<sub>3</sub> by UV light in the skin. Of course, vitamin D is also a nutrient present in



the diet as both vitamin D<sub>2</sub> (ergocalciferol) from plants and vitamin D<sub>3</sub> (cholecalciferol) from animals. The active hormonal 1,25(OH)<sub>2</sub>D<sub>3</sub> is generated by sequential enzymatic steps. The initial step in the liver is dependent on cholesterol 27-hydroxylase, CYP27, which produces 25(OH)D<sub>3</sub>. 25-Hydroxyvitamin D-1 $\alpha$ -hydroxylase (1 $\alpha$ -hydroxylase, CYP27B1) generates the active hormonal form in the kidney.

Levels of 1,25(OH)<sub>2</sub>D<sub>3</sub> are tightly regulated to maintain calcium homeostasis. VDR plays a central role in this process by both repressing expression of the proximal activator, 1 $\alpha$ -hydroxylase, and inducing expression of the inactivating enzyme CYP24, which produces 1,24,25-trihydroxyvitamin D<sub>3</sub>.

Based on their discovery that hydrophobic bile acids are also potent VDR agonists, Makishima et al. (2002) proposed that VDR has an additional function in the protection against the toxic and carcinogenic effects of these endobiotics in the gut.

#### *PXR and CAR*

These two related receptors are most commonly considered to respond to a wide range of potentially toxic foreign compounds, or xenobiotics. However, they can also be activated by a number of potentially toxic endogenous compounds (endobiotics). For PXR, bile acids, particularly more hydrophobic and toxic examples, such as lithocholic acid, function as direct agonists (Staudinger et al., 2001; Xie et al., 2001). PXR activation by elevated concentrations of such bile acids results in induction of cytochrome P450 enzymes that hydroxylate them and thereby decrease their toxicity. Murine PXR can also be activated by oxysterol precursors of bile acids (Goodwin et al., 2003).

CAR has both direct and indirect mechanisms of activation based on either conventional agonist binding or a still poorly characterized pathway of induced nuclear translocation (Swales and Negishi, 2004; Qatanani and Moore, 2005). In the latter case, the constitutive transactivation function of CAR results in induction of expression of appropriate target genes. There are no known endogenous agonists that directly activate CAR in physiologic pathways. The first CAR ligands identified were the endogenous androgen metabolites, androstanol and androsthenol, which are inverse agonists that can block the constitutive activity of CAR (Forman et al., 1998), but this requires micromolar concentrations that are far above those reached in vivo. CAR can be activated indirectly by high concentrations of both bile acids (Zhang et al., 2004) and bilirubin (Huang et al., 2003). Both of these pathways result in detoxification and induced clearance of these endogenous toxins. For both CAR and PXR, normal physiologic concentrations of these endobiotics cannot effectively activate the receptors. Instead, both function to protect against the consequences of pathologically elevated levels.

### **Synthetic Ligands and Selective Modulators**

#### *LXR $\alpha$ and $\beta$*

The majority of the studies of the effects of synthetic LXR agonists have been carried out with a single compound, T0901317, which activates both isoforms (Schultz et al., 2000). A number of effects have been reported for T0901317, primarily in mouse models, but the best characterized is an increase in reverse cholesterol transport. In this process, LXR activation in macrophages induces expression of the ATP-binding cassette transporters ABCA1 and G1 and increases transport of cholesterol to the acceptor apolipoprotein A1. The result is inhibition of atherogenesis in mouse models (Tangirala et al., 2002; Levin et al., 2005), and a similar beneficial effect has been described for another LXR pan-agonist, GW3965 (Joseph et al., 2002b).

Although LXR activation has desirable effects on reverse cholesterol transport and other potentially desirable effects, it also increases serum triglycerides in mouse models. This increase is believed to be related to the induction of SREBP-1c in the liver and is also thought to be primarily an LXR $\alpha$  function, raising the possibility that an LXR $\beta$ -specific agonist could retain many of the beneficial effects without the undesirable triglyceride effect.

#### *FXR $\alpha$*

FXR $\alpha$  responds to bile acids at their physiologic concentrations, in the range of 10 to 100  $\mu$ M (Makishima et al., 1999; Parks et al., 1999; Wang et al., 1999). This is a much lower affinity than that of classic steroid and thyroid hormone receptors and is associated with decreased specificity, which allows responses to structurally diverse conjugated and unconjugated bile acids. However, it also means that FXR $\alpha$  is a relatively non-specific receptor that can respond to a wide range of additional compounds. It is therefore relatively easy to identify novel modulators of FXR $\alpha$  activity, but the large majority of studies on synthetic FXR $\alpha$  ligands have focused on a single compound, GW4064. This potent FXR $\alpha$  agonist binds with high affinity and apparently good specificity, although its spectrum of effects on other potential targets remains to be established. More limited studies have been carried out with another synthetic agonist, fexaramine, and the synthetic bile acid derivative 6- $\alpha$ -ethyl-chenodeoxycholic acid. Like the LXRs, FXR $\alpha$  is a current target for the development of therapeutic agents. The effects of GW4064 and some other agonists in animal models provide support for potential applications in lowering triglycerides (Maloney et al., 2000) and protecting against liver damage in cholestasis (Liu et al., 2003) and cholesterol gallstone disease (Moschetta et al., 2004).

Consistent with the apparent flexibility of FXR $\alpha$ , other ligands seem to have more selective modulatory effects. The naturally occurring phytosteroids *E*- and

Z-guggulsterone were initially described as FXR $\alpha$  antagonists (Urizar et al., 2002) but may be selective modulators with different effects on different targets (Cui et al., 2003), and the synthetic ligand AGN34 reportedly also functions as an agonist or antagonist in different gene contexts (Dussault et al., 2003).

### VDR

1,25(OH) $_2$ D $_3$  itself provides a simple means for VDR activation and is clinically used in treatment of osteoporosis, psoriasis, and secondary hyperparathyroidism. However, the undesirable hypercalcemic effects of higher doses complicate these and a wide range of additional potential therapeutic applications in diverse areas that include immunology and cancer. In marked contrast with the other NR1I receptors CAR and PXR, VDR is a highly specific receptor. Thus, substantial effort has been directed to developing selective, noncalcemic 1,25(OH) $_2$ D $_3$  analogs (Nagpal et al., 2005). Although progress has been made, this problem has not been solved, and clinical use of selective VDR agonists is not yet widespread.

### PXR and CAR

These two receptors are unique among the NRs in that they are specifically designed to be nonspecific (Willson and Kliewer, 2002). They are not activated by specific hormones but instead can recognize and respond to an enormous range of relatively small, hydrophobic exogenous compounds. Direct binding of such compounds is the dominant mechanism of activation of PXR, which has a larger and more flexible ligand-binding pocket. PXR can be activated by an unknown fraction of the total number of relatively hydrophobic organic molecules with molecular masses roughly <1000 Da. Although the likelihood that a particular compound is a PXR agonist may be small, the enormity of this chemical space means that the number of such compounds is essentially unlimited. As noted above, CAR has a more restricted ligand-binding pocket and has a much more limited range of direct agonist ligands. However, this restriction is complemented by the indirect translocation mechanism in hepatocytes, which can be triggered by elevated levels of a very wide range of structurally unrelated compounds. These two receptors function together to regulate common target genes to promote xenobiotic detoxification, and their distinct mechanisms of activation are thought to facilitate response to an especially diverse range of xenobiotic stimuli.

Another unusual aspect of ligand binding by PXR and CAR is the high divergence of their ligand-binding domains between species, which leads to quite different ligand profiles. Thus, the antibiotic rifampicin is a potent agonist for human PXR but does not bind the rodent receptor (Lehmann et al., 1998). Similarly, the human CAR agonist CITCO is inactive against murine CAR (Maglich et al., 2003). As expected, "humanized" trans-

genic mouse strains expressing the human PXR or CAR instead of the endogenous receptor respond only to appropriate human agonists (Xie et al., 2000; Huang et al., 2004). The agonists most commonly used in studies of mouse PXR and CAR are PCN and TCPOBOP, respectively. Nuclear translocation of both human and mouse CAR can be induced by the widely used CAR activator phenobarbital.

Antagonists of PXR have not been well characterized. As noted above, however, the first murine CAR ligands identified are inverse agonists (Forman et al., 1998). More recently, the antifungal agent clotrimazole (Moore et al., 2000) and the anti-nausea agent meclizine (Huang et al., 2004) have been identified as human CAR inverse agonists. The functional divergence between species is highlighted by the fact that meclizine is a potent agonist for mouse CAR (Huang et al., 2004).

## Genetics

### LXR $\alpha$ and $\beta$

The genetics of the LXR isoforms in humans remains unexplored, with no hereditary diseases associated with LXR defects and not even any published reports on LXR gene polymorphisms. In mice, however, both the individual and the double LXR gene knockouts have been well studied. Loss of LXR $\alpha$  function results in a defect in cholesterol elimination, with the LXR $\alpha$ <sup>-/-</sup> livers accumulating much greater amounts of cholesterol than wild-type livers when the mice were challenged with a high cholesterol diet (Peet et al., 1998). The loss of LXR $\beta$  does not result in a similar defect, but the combined loss of both isoforms exacerbates the cholesterol elimination defect of the LXR $\alpha$ <sup>-/-</sup> mice (Laffitte et al., 2001).

The role of LXR isoforms in reverse cholesterol transport was confirmed in mice with selective loss of both isoforms in macrophages, which was accomplished by transplant of double knockout bone marrow into irradiated hosts. In atherogenic models, animals receiving the mutant cells developed much more atherosclerosis than those transplanted with wild-type cells and were also resistant to the antiatherogenic effect of the LXR agonist T0901317 (Tangirala et al., 2002; Levin et al., 2005). Atherogenesis is associated with inflammation, and similar transplants also revealed direct functions for LXRs in inhibiting expression of proinflammatory genes and activating innate immunity (Joseph et al., 2003, 2004).

The other major role of LXR isoforms is in lipid homeostasis as evidenced by resistance to diet-induced obesity seen in LXR double knockout mice (Kalaany et al., 2005). This phenotype is due to loss of hepatic triglyceride synthesis and the uncoupled burning of dietary fat in the periphery.

### FXR $\alpha$ and $\beta$

The mouse genome encodes two FXR types, FXR $\alpha$  and FXR $\beta$  (Otte et al., 2003). Remarkably, human FXR $\beta$  is a

pseudogene, with numerous nucleotide changes that preclude expression of the intact protein. Essentially nothing is known about the function of mouse FXR $\beta$ . A further complication is that the conserved FXR $\alpha$  (generally termed FXR) gene encodes four protein products (Zhang et al., 2003). Because of differential promoter usage, FXR $\alpha$ 3 and FXR $\alpha$ 4 have 37 additional N-terminal amino acids that are not present in FXR $\alpha$ 1 and FXR $\alpha$ 2. Because of differential splicing, FXR $\alpha$ 1 and FXR $\alpha$ 3 have an additional four amino acids in the hinge region that are not present in FXR $\alpha$ 2 and FXR $\alpha$ 4. There is evidence for functional differences between these very similar proteins, but their potentially distinct physiologic roles remain to be determined.

As with the LXRs, human genetics of FXR $\alpha$  is in its infancy. However, loss of FXR $\alpha$  function in mice results in profound defects in bile acid metabolism, notably a failure to suppress their production in response to elevated bile acid levels (Sinal et al., 2000). The FXR $\alpha$ -deficient mice also have defects in cholesterol homeostasis (Lambert et al., 2003) and accumulate lipids in the liver and in circulation (Sinal et al., 2000). Recent results indicate that the elevated liver and serum lipids result in insulin resistance (Cariou et al., 2006; Ma et al., 2006; Zhang et al., 2006).

## VDR

The vitamin D receptor was the first NR gene for which human mutations were identified (Hughes et al., 1988) and remains the only member of the NR1 subgroup for which clear loss of function mutations have been characterized. Disruption of VDR function due to either VDR gene mutation or the absence of the 1,25(OH) $_2$ D $_3$  ligand leads to rickets (Kato et al., 2002). The disease has a number of manifestations associated with dysregulation of calcium homeostasis, including muscle weakness, growth retardation, and bone deformity, along with secondary hyperparathyroidism and aminoaciduria. Some patients come to medical attention because of convulsions or tetany. VDR mutations are the molecular basis for vitamin D-dependent rickets type II, which is also known as hypocalcemic vitamin D-resistant rickets. Patients with vitamin D-dependent rickets type II have elevated circulating levels of 1,25(OH) $_2$ D $_3$ , and because of the receptor defect, physiologic doses of 1,25(OH) $_2$ D $_3$  are unable to resolve the disease in its most severe forms. Less severe forms associated with decreased rather than absent receptor functions can be treated with elevated levels of 1,25(OH) $_2$ D $_3$ .

VDR knockout mice have been generated by multiple groups (Li et al., 1997; Yoshizawa et al., 1997; Van Cromphaut et al., 2001; Zeitz et al., 2003). These mice are relatively normal until weaning but show a wide range of phenotypes also observed in vitamin D deficiency. Thus, the knockouts fail to thrive and show alopecia, infertility, hypocalcemia, and severely impaired bone formation. Female mice have uterine hypoplasia

and impaired folliculogenesis. VDR-null animals generally die before 4 months of age. Remarkably, however, the pathologic impact of the loss of VDR function is substantially ameliorated by feeding diets rich in calcium, phosphate, and lactose (Amling et al., 1999), indicating that many of these effects are due to dysregulation of mineral homeostasis.

## PXR and CAR

Polymorphisms that may have functional effects have been identified for both PXR and CAR (Koyano et al., 2004; Ikeda et al., 2005; Lamba et al., 2005) but genetic variation in humans has not yet been associated with specific phenotypes. Mouse knockouts for PXR (Xie et al., 2000) or CAR (Wei et al., 2000) show the expected deficits in specific xenobiotic induction of drug metabolism and are also sensitive to elevated levels of endobiotic stress. Neither the single knockouts nor the double knockout exhibit obvious phenotypes under basal circumstances, indicating that these receptors function primarily to respond to chemical stresses.

The induction of drug metabolism is an undesirable drug side effect because the activation of this process by one therapeutic agent can dramatically alter the biologic activity of others that are coadministered. The divergence of the xenobiotic receptor ligand binding domains means that such drug-drug interactions relevant to humans cannot be reliably studied in standard rodent models. As noted above, however, lines of "humanized" mice expressing the human receptors instead of their mouse counterparts can be used to identify such effects (Xie et al., 2000; Zhang et al., 2002).

Tables 2 through 8 summarize the functions, biologic activities, structural properties, and ligands of these receptors.

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TABLE 2  
CAR

Receptor Nomenclature	NR1I3
Receptor code	4.10.1.XE:1:I3
Other names	MB67
Molecular information	Hs: 348aa, Q14994, chr. 1q23.3 <sup>1</sup> Rn: 358aa, Q9QUS1, chr. 13q24 Mm: 358aa, Q3V008, chr. 1 H3 <sup>2</sup>
DNA binding	
Structure	Heterodimer, RXR partner
HRE core sequence	AGGTCA (DR4, DR5, palindrome) <sup>1,3-5</sup>
Partners	
Agonists	TCPOBOP (20 nM),* meclizine (25 nM), CITCO (49 nM), pregnanedione (670 nM) [EC <sub>50</sub> ] <sup>14,6-8</sup>
Antagonists	Androstanol (400 nM), androstenol (400 nM), meclizine (69 nM), clotrimazole (690 nM) [IC <sub>50</sub> ] <sup>6,8,9</sup>
Coactivator	NCOA1, PPARBP, PGC-1 <sup>9-11</sup>
Corepressor	
Biologically important isoforms	CAR1 (Mm): main isoform in mouse <sup>2</sup> ; CAR2 (Mm): truncated form, lacking C-terminal sequence <sup>2</sup>
Tissue distribution	Liver, low levels in the kidney, intestine, stomach {Hs, Mm} [Northern blot, Q-PCR, immunohistology] <sup>1,2,12,13</sup>
Functional assay	Liver hepatomegaly after PB or TCPOBOP treatment {Mm} <sup>14,15</sup> ; drug clearance: recovery from zoxazolamine-induced paralysis {Mm} <sup>15</sup> ; acetaminophen liver toxicity {Mm} <sup>15</sup>
Main target genes	Activated: cytochrome P450 genes {Hs, Mm, Rn}, <sup>16</sup> <i>Mdm2</i> {Mm}, <sup>14</sup> <i>MRP2</i> {Mm} <sup>5</sup>
Mutant phenotype	Impaired drug metabolism induced by specific xenobiotics; resistance to chronic xenobiotic stress-induced liver tumorigenesis {Mm} [knockout] <sup>14,15</sup> ; responsive to human CAR ligands {Mm} [human CAR transgenic with CAR knockout background] <sup>17</sup>
Human disease	

aa, amino acids; chr., chromosome; HRE, hormone response element; PPARBP, PPAR-binding protein; Q-PCR, quantitative polymerase chain reaction; PB, phenobarbital.

\* Radioligand.

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TABLE 3  
PXR

Receptor Nomenclature	NR1I2
Receptor code	4.10.1.XE:1:I2
Other names	ONR1, BXR, PAR, PRR, PXR, SAR, PAR1, PAR2, PARq
Molecular information	Hs: 434aa, O75469, chr. 3q12-q13.3 <sup>1-3</sup> Rn: 431aa, Q9R1A7, chr. 11q21 <sup>4</sup> Mm: 431aa, O54915, chr. 16 B3 <sup>3</sup>
DNA binding	
Structure	Heterodimer, RXR partner
HRE core sequence	AGGTCA (DR-3, ER6, DR-4, ER8, IR0, PBRE) <sup>3,5-11</sup>
Partners	PIT1 (physical): cellular localization <sup>12</sup>
Agonists	Hyperforin (27 nM), SR12813 (200 nM), pregnenolone-16 $\alpha$ -carbonitrile (300 nM), (+)-S20 (0.4 $\mu$ M), dexamethasone (0.8 $\mu$ M), schisandrins A and B (1.25–2 $\mu$ M), rifampicin (0.8–3 $\mu$ M), 5 $\beta$ -cholestane-3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -triol (3–5 $\mu$ M), taxol (5 $\mu$ M) [EC <sub>50</sub> ] <sup>13-20</sup> ; lithocholic acid (9–15 $\mu$ M)* [IC <sub>50</sub> ] <sup>11</sup> ; vitamin K <sup>21</sup>
Antagonists	Ecteinascidin 743 (3 nM)[IC <sub>50</sub> ] <sup>18</sup>
Coactivators	NCOA1, NRIP1, PGC-1, FOXO1, GRIP1 <sup>3,22-25</sup>
Corepressors	SHP, NCOR2 <sup>18,26,27</sup>
Biologically important isoforms	PXR1 {Hs}: main isoform <sup>1,2,5</sup> ; PXR2 {Hs}: has a different 5'-UTR and encodes a single full-length product with an N-terminal extension not found in other isoforms; PXR3 {Hs}: has a different 5'-UTR and encodes an isoform lacking 39 N-terminal and 37 internal amino acids compared with PXR2—the reading frame is maintained, and it uses a non-AUG translation initiation codon
Tissue distribution	Liver, intestine, kidney, lung {Hs, Mm} [Northern blot, Q-PCR, immunohistology] <sup>1-5,13</sup>
Functional assays	Drug clearance by the liver following tribromoethanol-induced anaesthesia or zoxazolamine-induced paralysis {Mm} <sup>28</sup> ; measurement of bile acid liver toxicity after PXR activation {Mm} <sup>13,29</sup> ; bilirubin and corticosterone clearance {Mm} <sup>30</sup> ; warfarin clearance from the liver by PXR-activating Chinese herb wu wei zi ( <i>Schisandra chinensis</i> Baill) and gan cao ( <i>Glycyrrhiza uralensis</i> Fisch) {Rn} <sup>20</sup>
Main target genes	Activated: cytochrome P450 genes {Hs, Mm, Rn}, <sup>1-3,10,11,18,28,31</sup> <i>OATP2</i> {Mm, Rn}, <sup>32</sup> <i>MRP2</i> {Hs, Mm}, <sup>7</sup> <i>UGT1A1</i> {Mm}, <sup>30</sup> <i>SULT2A</i> {Mm}, <sup>8</sup> <i>MDR1</i> {Mm}, <sup>6</sup> <i>ALAS-1</i> {Mm} <sup>33</sup>
Mutant phenotype	Impaired drug metabolism induced by specific xenobiotics, such as loss of CYP3A11 inducibility in response to PCN and dexamethasone—sensitivity to bile acid-induced toxicity {Mm} [knockout] <sup>15,28,29</sup> ; acquired responsiveness to human-specific ligands such as rifampicin, loss of responsiveness to rodent-specific ligands, such as PCN {Mm} [hPXR transgenic mice and hPXR transgenic with PXR knockout background] <sup>28</sup> ; increased bilirubin and cortisone clearance, increased detoxification of bile acids, increased protection against xenobiotic toxicants, such as zoxazolamine and tribromoethanol {Mm} [transgenes of a constitutively activated hPXR into the liver] <sup>28-30</sup>
Human disease	Breast cancer: levels of PXR mRNA in ER-positive tumors are significantly lower than those observed in ER-negative tumors <sup>34</sup> ; a significant positive correlation was detected between SXR/hPXR labeling index and both the histologic grade and the lymph node status of the carcinomas <sup>35</sup>

aa, amino acids; chr., chromosome; HRE, hormone response element; PAR, proliferator-activated receptor; UTR, untranslated region; Q-PCR, quantitative polymerase chain reaction; h, human; ER, estrogen receptor; BXR, benzoate X receptor; PBRE, phenobarbital response element.

\* Radioligand.

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TABLE 4  
FXR

Receptor Nomenclature	NR1H4
Receptor code	4.10.1:BA:1:H4
Other names	BAR, HRR1, RIP14
Molecular information	Hs: 486aa, Q96R11, chr. 12q23.1 Rn: 469aa, Q62735, chr. 7q13 <sup>1</sup> Mm: 488aa, Q60641, chr. 10 C2 <sup>2</sup>
DNA binding	
Structure	RXR partner
HRE core sequence	AGTTTCAnTGAAC T
Partners	
Agonists	GW4064 (15 nM), fexaramine (250 nM), 22(R)-hydroxycholesterol (>3 μM), lithocholic acid (5 μM), chenodeoxycholic acid (5 μM), cholic acid (>10 μM), deoxycholic acid (100 μM), [EC <sub>50</sub> ] <sup>3-8</sup> Guggulsterone (10 μM) [IC <sub>50</sub> ] <sup>9</sup>
Antagonists	
Coactivator	
Corepressor	
Biologically important isoforms	FXRα 1 {Hs, Mm} <sup>2,10,11</sup> ; FXRα 2 {Hs, Mm} <sup>2,10,11</sup> ; FXRα 3 {Hs, Mm} <sup>2,10,11</sup> ; FXRα 4 {Hs, Mm} <sup>2,10,11</sup>
Tissue distribution	Liver, small intestine, colon, kidney, adrenal gland {Mm, Rn} [Northern blot, Q-PCR, in situ hybridization] <sup>1,2,11</sup>
Functional assay	
Main target genes	Activated: <i>FGF19</i> {Hs}, <sup>12</sup> <i>FGF15</i> {Mm}, <sup>13</sup> <i>SHP</i> {Hs, Rn, Mm}, <sup>14,15</sup> <i>BSEP</i> {Hs, Rn, Mm}, <sup>16</sup> <i>IBABP</i> {Hs, Mm}, <sup>17</sup> <i>MDR3</i> {Hs}, <sup>18</sup> <i>Mdr2</i> {Rn, Mm}, <sup>19,20</sup> <i>MRP2</i> {Hs, Rn}, <sup>21</sup> <i>OATP1B3</i> {Hs}, <sup>22</sup> <i>BACS</i> {Hs, Rn}, <sup>23</sup> <i>ApoCII</i> {Hs, Mm}, <sup>24</sup> <i>C3</i> {Hs}, <sup>13</sup> <i>PDK4</i> {Hs, Rn, Mm}, <sup>25</sup> <i>PLTP</i> {Hs, Mm}, <sup>9</sup> <i>PPARα</i> {Hs}, <sup>26</sup> <i>αA-crystallin</i> {Hs}, <sup>27</sup> fibrinogen {Hs}, <sup>28</sup> kininogen {Hs}, <sup>18</sup> syndecan-1 {Hs}, <sup>4</sup> <i>VPAC1</i> {Hs}, <sup>29</sup> <i>OSTα</i> and <i>OSTβ</i> {Hs} <sup>30-32</sup> ; repressed: <i>CYP7A1</i> {Hs, Rn, Mm}, <sup>14,15</sup> <i>ABAT</i> {Hs, Mm}, <sup>33,34</sup> <i>NTCP</i> {Rn, Mm}, <sup>35</sup> <i>APOAI</i> {Hs}, <sup>36,37</sup> <i>ApoCIII</i> {Hs, Mm}, <sup>36</sup> hepatic lipase {Hs}, <sup>38</sup> <i>SREBP-1c</i> {Mm}, <sup>39</sup> <i>VLDLR</i> {Hs, Mm} <sup>40</sup>
Mutant phenotype	Elevated serum bile acids, cholesterol and triglycerides; increased hepatic cholesterol and triglycerides; proatherogenic serum lipoprotein profile; reduced bile acid pools and reduced fecal bile acid secretion {Mm} [knockout] <sup>41,42</sup>
Human disease	

aa, amino acids; chr., chromosome; HRE, hormone response element; Q-PCR, quantitative polymerase chain reaction; BAR, bile acid receptor; SHP, small heterodimer partner; BSEP, bile salt export pump; IBABP, ileal bile acid-binding protein; BACS, bile acid-CoA synthetase; PLTP, phospholipid transfer protein; OST, organic solute transporter; ABAT, apical bile acid transporter; NTCP, sodium/taurocholate cotransporting polypeptide; APOAI, apolipoprotein A-I; VLDLR, very-low-density lipoprotein receptor.

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TABLE 5  
*FXR $\beta$* 

Receptor Nomenclature	NR1H5
Receptor code	4.10.1:BA:1:H5
Other names	
Molecular information	Hs: Mm: 505aa, Q80ST6, chr. 3 F2.2 <sup>1</sup>
DNA binding	
Structure	Heterodimer
HRE core sequence	AGTTCA N TGAAC T (ER2)
Partners	
Agonists	Lanosterol (1 $\mu$ M), vitamin D <sub>3</sub> (10 $\mu$ M), cholesten (10 $\mu$ M), desmosterol (10 $\mu$ M) [EC <sub>50</sub> ] <sup>1</sup>
Antagonists	
Coactivator	NCOA1 <sup>1</sup>
Corepressor	
Biologically important isoforms	FXR $\beta$ -isoform 1 {Mm} <sup>1</sup> ; FXR $\beta$ -isoform 2 {Mm}: splice variant in exon 8 <sup>1</sup> ; FXR $\beta$ -isoform 3 {Mm}: splice variant in exon 10, lacking exon 11 <sup>1</sup> ; FXR $\beta$ -isoform 4 {Mm}: splice variants in exon 8 and 10, lacking exon 11 <sup>1</sup> ; FXR $\beta$ -isoform 5 {Mm}: splice variant in exon 3 <sup>1</sup>
Tissue distribution	Ubiquitous {Mm} [RT-PCR] <sup>1</sup>
Functional assay	
Main target genes	
Mutant phenotype	
Human disease	

aa, amino acids; chr., chromosome; HRE, hormone response element; RT-PCR, reverse transcriptase-polymerase chain reaction.

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TABLE 6  
LXR $\alpha$ 

Receptor Nomenclature	NR1H3
Receptor code	4.10.1.OXY:1:H3
Other names	LXR-a, RLD-1
Molecular information	Hs: 447aa, Q13133, chr. 11p11.2 <sup>1</sup> Rn: 445aa, Q62685, chr. 3q24 <sup>2</sup> Mm: 445 aa, Q9Z0Y9, chr. 2 E1 <sup>3</sup>
DNA binding	
Structure	RXR partner
HRE core sequence	AGGTCANNNNAGGTCA (DR-4)
Partners	RXR (physical, functional): required for transactivation <sup>1</sup> ; SHP (physical, functional): represses transactivation <sup>4</sup> ; LRH-1 (functional): competence factor <sup>5</sup>
Agonists	Acetyl-podocarpic dimer (1 nM), T0901317 (50 nM), 27-hydroxycholesterol (85 nM), GW3965 (190 nM), 24(S)-hydroxycholesterol (4 $\mu$ M), 24(S),25-epoxycholesterol (4 $\mu$ M), paxilline (4 $\mu$ M), 22(R)-hydroxycholesterol (5 $\mu$ M) [EC <sub>50</sub> ] <sup>6-12</sup> ; F(3)methylAA (13 nM) [K <sub>d</sub> ] <sup>13</sup>
Antagonists	
Coactivator	NCOA1, p300, TRRAP, GRIP1/TIF2, PGC1a, PGC1b <sup>14-18</sup>
Corepressor	NCOR1, NCOR2 <sup>19</sup>
Biologically important isoforms	
Tissue distribution	Liver, small intestine, kidney, adipose tissue, macrophages, spleen, adrenal gland {Rn} [Northern blot] <sup>1</sup>
Functional assay	
Main target genes	Activated: ABCA1 {Hs}, <sup>20,21</sup> ABCG1 {Hs}, <sup>22,23</sup> SREBP1c {Hs}, <sup>24</sup> APOC1/IV/II {Hs}, <sup>25</sup> APOE {Hs}, <sup>26</sup> APOD {Hs}, <sup>27</sup> CETP {Hs}, <sup>5</sup> LPL {Hs}, <sup>28</sup> PLTP {Hs}, <sup>29,30</sup> Cyp7A {Mm}, <sup>10</sup> FAS {Hs}, <sup>31</sup> GLUT4 {Hs} <sup>32</sup>
Mutant phenotype	Inability to tolerate dietary cholesterol; accumulation of hepatic cholesteryl esters resulting in hepatomegaly; increased serum LDL; decreased serum HDL, VLDL, and triglycerides {Mm} [knockout] <sup>11,33,34</sup> ; resistant to obesity when challenged with a diet containing high fat and cholesterol {Mm} [knockout] <sup>35</sup>
Human disease	

aa, amino acids; chr., chromosome; HRE, hormone response element; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein; TRRAP, transformation/transcription domain-associated protein; APOC, apolipoprotein C; APOE, apolipoprotein E; APOD, apolipoprotein D; CETP, cholesteryl ester transfer protein; LPL, lipoprotein lipase; PLTP, phospholipid transfer protein; FAS, fatty acid synthase.

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TABLE 7  
LXR $\beta$ 

Receptor Nomenclature	NR1H2
Receptor code	4.1.1:OXY:1:H2
Other names	LXR-b, UNR, OR-1, NER, NER1, RIP15
Molecular information	Hs: 461aa, P55055, chr. 19q13.3 <sup>1</sup> Rn: 446aa, Q62755, chr. 1q22 <sup>2</sup> Mm: 446aa, Q60644, chr. 7 B3 <sup>3</sup>
DNA binding	
Structure	RXR partner
HRE core sequence	AGGTCANNNNAGGTCA (DR-1, DR-4)
Partners	RXR (physical) <sup>3</sup> ; SHP (physical, functional) <sup>4</sup>
Agonists	Acetyl-podocarpic dimmer (1 nM), GW3965 (30 nM), T0901317 (50 nM), 27-hydroxycholesterol (71 nM), 22(R)-hydroxycholesterol (3 $\mu$ M), 24(S)-hydroxycholesterol (3 $\mu$ M), 24(S),25-epoxycholesterol (3 $\mu$ M),* paxilline (4 $\mu$ M), [EC <sub>50</sub> ] <sup>5-11</sup> ; F(3)methylAA (7 nM) [K <sub>d</sub> ] <sup>12</sup>
Antagonists	
Coactivator	NCOA1, p300 <sup>13</sup>
Corepressor	NCOR1, NCOR2 <sup>14</sup>
Biologically important isoforms	
Tissue distribution	Ubiquitous {Rn} [Northern blot] <sup>2,15</sup>
Functional assay	
Main target genes	Activated: <i>ABCA1</i> {Hs}, <sup>16,17</sup> <i>ABCG1</i> {Hs}, <sup>18,19</sup> <i>SREBP1c</i> {Hs}, <sup>20</sup> <i>APOC1/IV/II</i> {Hs}, <sup>21</sup> <i>APOE</i> {Hs}, <sup>22</sup> <i>CETP</i> {Hs}, <sup>23</sup> <i>Cyp7A</i> {Mm}, <sup>9</sup> <i>FAS</i> {Hs}, <sup>24</sup> <i>GLUT4</i> {Hs} <sup>25</sup>
Mutant phenotype	Alterations in adipocyte growth, glucose homeostasis, and $\beta$ -cell function (normal resistance to dietary cholesterol, unlike the LXR $\alpha$ knockout) {Mm} [knockout] <sup>26,27</sup>
Human disease	

aa, amino acids; chr., chromosome; HRE, hormone response element; UNR, ubiquitously expressed nuclear receptor; APOC, apolipoprotein C; APOE, apolipoprotein E; CETP, cholesteryl ester transfer protein; FAS, fatty acid synthase.

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TABLE 8  
VDR

Receptor Nomenclature	NR1I1
Receptor code	
Other names	
Molecular information	Hs: 427aa, P11473, chr. 12q13.11 <sup>1</sup> Rn: 423aa, P13053, chr. 7q36 <sup>2</sup> Mm: 422aa, P48281, chr. 15 F1 <sup>3</sup>
DNA binding	
Structure	Heterodimer, RXR partner
HRE core sequence	DR-3
Partners	
Agonists	KH1060 ( $6.5 \times 10^{-11}$ M), EB1089 ( $2.7 \times 10^{-10}$ M), $1\alpha, 25\text{-(OH)}_2\text{D}_3$ ( $6.2 \times 10^{-10}$ M),* 25-OHD <sub>3</sub> ( $1.2 \times 10^{-9}$ M), (23S,25R)- $1\alpha, 25\text{-(OH)}_2\text{D}_3\text{-26,23-lactone}$ ( $3.1 \times 10^{-8}$ M) [ $K_d$ ] <sup>4-7</sup> ; 2MD ( $1 \times 10^{-10}$ M) [ED <sub>50</sub> ] <sup>8</sup> ; MC903 (131), TV-02 (66), F <sub>6</sub> - $1\alpha, 25\text{(OH)}_2\text{D}_3$ (45), Gemini [ $1R, 25\text{-dihydroxy-21-(3-hydroxy-3-methylbutyl)vitamin D}_3$ ] (38), OCT (10) [RCI] <sup>5,9-13</sup> ; Ro-26-9228 ( $6.2 \times 10^{-9}$ M) [IC <sub>50</sub> ] <sup>14</sup> ; LG190178 ( $1.5 \times 10^{-7}$ M), 3-keto-LCA ( $2.9 \times 10^{-7}$ M), LCA ( $8 \times 10^{-6}$ M) [ $K_i$ ] <sup>15,16</sup> ; ED-71, $1\alpha\text{-OHD}_2$ , 19-nor- $1\alpha, 25\text{(OH)}_2\text{D}_2$ <sup>17,18</sup> TEI-9647 (10), ZK159222 (7) [RCI] <sup>19,20</sup>
Antagonists	
Coactivator	
Corepressor	
Biologically important isoforms	
Tissue distribution	
Functional assay	
Main target genes	
Mutant phenotype	Knockout mice exhibit typical rachitic features such as hypocalcemia, hyperparathyroidism, impaired bone formation, uterine hypoplasia, growth retardation, and alopecia after weaning; they also have an impaired insulin secretory capacity [Mm] [knockout <sup>21-23</sup> ]
Human disease	Vitamin D-dependent rickets type II <sup>24,25</sup>

aa, amino acids; chr., chromosome; HRE, hormone response element; OCT, 22-oxa- $1\alpha, 25\text{-dihydroxyvitamin-D}_3$ ; LCA, lithocholic acid; RCI, relative competitive index.  
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