X-ray Crystal Structure of the Liver X Receptor β Ligand Binding Domain

REGULATION BY A HISTIDINE-TRYPTOPHAN SWITCH*

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Shawn Williams‡, Randy K. Bledsoe, Jon L. Collins, Sharon Boggs, Millard H. Lambert, Ann B. Miller§, John Moore, David D. McKee, Linda Moore, Jason Nichols, Derek Parks, Mike Watson, Bruce Wisely, and Timothy M. Willson

From GlaxoSmithKline, Discovery Research, Research Triangle Park, NC 27709

The x-ray crystal structures of the human liver X receptor β ligand binding domain complexed to sterol and nonsterol agonists revealed a perpendicular histidine-tryptophan switch that holds the receptor in its active conformation. Hydrogen bonding interactions with the ligand act to position the His-435 imidazole ring against the Trp-457 indole ring, allowing an electrostatic interaction that holds the AF2 helix in the active position. The neutral oxysterol 24(S),25-epoxycholesterol accepts a hydrogen bond from His-435 that positions the imidazole ring of the histidine above the pyrrole ring of the tryptophan. In contrast, the acidic T0901317 hydroxyl group makes a shorter hydrogen bond with His-435 that pulls the imidazole over the electron-rich benzene ring of the tryptophan, possibly strengthening the electrostatic interaction. Point mutagenesis of Trp-457 supports the observation that the ligand-histidine-tryptophan coupling is different between the two ligands. The lipophilic liver X receptor ligand-binding pocket is larger than the corresponding steroid hormone receptors, which allows T0901317 to adopt two distinct conformations. These results provide a molecular basis for liver X receptor activation by a wide range of endogenous neutral and acidic ligands.

The liver X receptors, LXRα (NR1H3) and LXRβ (NR1H2), are transcription factors belonging to the nuclear receptor superfamily that function as intracellular receptors for oxygenated cholesterol metabolites, known as oxysterols (1–3). The LXRα function as heterodimers with the retinoid X receptor to regulate the important aspects of cholesterol homeostasis through their target genes, which include the ATP binding cassette ABCA1 (4–6) and CYP7A1 (2, 3). One of the most potent endogenous activators of LXR in the liver is 24(S),25-epoxycholesterol (eCH) (Fig. 1a) (2, 7), a unique oxysterol generated by a shunt pathway from squalene that is activated upon cholesterol feeding (8, 9). Synthetic nonsterol LXR agonists have also been identified, including T0901317 (T1317) (10), a lipophilic tertiary sulfonamide that contains an acidic bis-trifluoromethyl carbonyl group (Fig. 1a).

Nuclear receptors regulate transcription through the recruitment of coactivator proteins to the ligand binding domain (LBD) (11). Structural and biochemical studies reveal that the coactivator contains a short α-helical LXXLL sequence (where X = any amino acid), known as an NR box, that binds the nuclear receptor LBD. The NR box is capped by a charge clamp on the surface of the LBD formed by a lysine on helix 3 and a glutamic acid on the C-terminal AF2 helix (12). Despite the availability of multiple co-crystal structures of ligand/receptor complexes, the mechanism by which small molecule ligands activate nuclear receptors is still poorly understood (13). We have shown previously that a residue in the AF2 helix of LXRα, Trp-443, plays a role in the activation of the receptor by oxysterols (14). Based on these results, we proposed a model where the AF2 helix was stabilized in its active conformation by a hydrogen bond from the tryptophan indole NH to the sterol agonist (14). Interestingly, both the neutral sterol eCH and the acidic nonsterol T1317 are efficacious activators of LXRα and LXRβ in biochemical and cell-based assays (Fig. 1, b and c). To probe the molecular basis by which both sterol and nonsterol agonists regulate LXR activity, we initiated crystallographic investigations of both LXRα and LXRβ LBD. Diffracting crystals of the LXRβ LBD complexed to eCH and T1317 were readily obtained, allowing us to determine those structures.

EXPERIMENTAL PROCEDURES

LXRα Expression and Purification—A construct of human LXRα LBD (ligand binding domain) containing amino acids 214–461 and an N-terminal thrombin cleavable His tag was subcloned into the Escherichia coli expression vector pRSETa (Invitrogen) and expressed in BL21(DE3). All subsequent steps are at 4 °C. Cells were resuspended in NiA (25 mM imidazole, pH 8.0, 150 mM NaCl, 3% 1,2-propanediol) and then lysed using a cell homogenizer (Rannie) followed by clarification by centrifugation.

The soluble protein was loaded onto the pre-equilibrated nickel-nitrilotriacetic acid affinity column (Qiagen) following elution with a 10-column volume 50–500 mM imidazole gradient. Peak fractions were pooled and dialyzed versus 10 mM Tris, pH 8.0, 150 mM NaCl, 0.1 mM EDTA, 5% glycerol.

Protein was further purified using anion exchange. His-tagged LXR was digested overnight with thrombin at a mass ratio of 1:500. The digested protein was diluted to 25 mM salt with Q0 (10 mM Tris, pH 8.0, 0.1 mM EDTA, 5% glycerol, 5 mM dithiothreitol), loaded onto the pre-equilibrated anion exchange column, and eluted by a 20-column 0–250 mM NaCl gradient. LXR eluted as two peaks at ~150 mM NaCl, which were kept separate for crystallization trials. The eluted protein was dialyzed versus 10 mM Tris, pH 8.0, 0.1 mM EDTA, 5% glycerol, 5 mM
dithiothreitol, 150 mM NaCl, eCH, and SRC1, or T1317 was added, and the protein was concentrated to 12–14 mg/ml for crystallization trials. **Crystallization and Structure Determination**—Crystallization trials were carried out using the hanging drop method by mixing 2 μl of protein solution with 2 μl of well buffer. LXRβ/T1317 complexes crystallized from 10 to 20% polyethylene glycol 3350 with 100 mM concentration of a number of salts, including NaF, KF; NaCl, KCl, sodium formate, sodium acetate, and potassium acetate at 4 °C. LXRβ/eCH/SRC1 complexes crystallized from 10 to 12% polyethylene glycol 3350–8000 with 0.2 mM NaCl at 4 °C. Crystals took 4–6 weeks to grow. Crystals were frozen in LN2 after transferring stepwise to a cryo buffer containing the well buffer with 30% polyethylene glycol 400.

All data were obtained at the Industrial Macromolecular Crystallography Association Collaborative Access Team (IMCA CAT) 17 ID beam line at the Advanced Photon Source at a wavelength of 1 Å on a MAR CCD detector. Crystals of the LXRβ/T1317 complex diffracted to 2.3 Å and were in the space group P2_1 2_1 2_1 with unit cell parameters a = 60.25, b = 82.454, c = 123.175. Crystals of the LXRβ/eCH/SRC1 complex diffracted to 2.7 Å and were in the space group P2_1 2_1 2_1, with lattice constants of a = 71.17 Å, b = 120.01 Å, c = 147.56 Å. All diffraction data were integrated and scaled using HKL2000 (15). The LXRβ/T1317 structure was solved by molecular replacement using the program AMoRe with a truncated monomeric form of human retinoic acid receptor-γ as a search model. The LXRβ/eCH/SRC1 structure was solved by molecular replacement using a refined LXR subunit from the LXRβ/T1317 structure as a search model. For both complexes, there were two molecules in the asymmetric unit related by a noncrystallographic dyad. Noncrystallographic averaging was utilized during refinement. Structures were subjected to multiple rounds of building using Quanta and refined using CNX and Refmac5.

**Biological Assays**—LXR cell-free ligand sensing assays and LXR cell-based transactivation assays were performed as described previously (14).

**Chemical Compounds**—T1317 and eCH were synthesized as described previously (10, 16). The T-CH hybrid was synthesized from chlord-e-en-24-4-al by addition of (trifluoromethyl)trimethylsilane catalyzed by tetrabutylammonium fluoride, oxidation with Dess-Martin chlol-5-en-24-al by addition of (trifluoromethyl)trimethylsilane catalyzed previously (10, 16). The T-CH hybrid was synthesized from previously (13, 14), and refined using CNX and Refmac5.

**Structure Determination**—The human LXRβ LBD (residues 214–461) was crystalized in complex with T1317 or with eCH and a peptide from the coactivator SRC1. Crystals of the LXRβ/T1317 complex diffracted to 2.3 Å, whereas the LXRβ/eCH/SRC1 complex diffracted to 2.7 Å (Table I). The LXRβ LBD had the anticipated three-layered α-helical fold seen for other nuclear receptors (13). The most distinguishing features of the LXRβ structure were a long helix 1 (18 residues) and a relatively large ligand binding pocket (830 Å³) as compared with the classic steroid hormone receptors (420–550 Å³). In both structures, the asymmetric unit contained an LXRβ homodimer, where each monomer was occupied by a single ligand (Fig. 2). The dimer interface was composed of residues in helices 7, 9, and 10 and is similar to other homo- and heterodimer interfaces (13). In the eCH structure, the Ca atoms in the two subunits have a root mean squared deviation of 0.4 Å, whereas in the T1317 structure, the Co atoms have a root mean squared deviation of 0.6 Å.

In the eCH/LXRβ complex, the sterol bound with the A-ring oriented toward helix 1 and with the D-ring and epoxide tail oriented toward the C-terminal end of helix 10, Trp-457, and His-435 (Fig. 3a). This orientation was similar to that predicted in the model of Spencer et al. (14) and was similar to that of estradiol, progesterone, and dexamethasone in their complexes with the estrogen, progesterone, and glucocorticoid receptors. However, the steroid core of eCH was flipped 180° around its long axis so that the angular methyl groups pointed in the direction opposite that in the steroid hormones (Fig. 3a). Although the epoxide oxygen atom lay adjacent to Trp-457, it actually made its hydrogen bond with the imidazole ring of His-435. The A-ring hydroxyl formed a hydrogen bond with Glu-281 on helix 3 and was positioned close to Arg-319 on helix 5. This is reminiscent of the estradiol/estrogen receptor complex, where the phenolic A-ring hydroxyl makes strong hydrogen bonds with Glu-353 on helix 3 and Arg-394 on helix 5 (17). However, in LXRβ, the A-ring hydroxyl group lay out of the plane of the Arg-319 guanidinium group, and despite its favorable distance, cannot make a hydrogen bond with good geometry. In addition to these polar interactions, eCH also made extensive lipophilic interactions with the ligand binding pocket, and its conformation was essentially the same in both subunits. In the T1317/LXRβ structure, the acidic carboxyl group lay in approximately the same position as the epoxide of eCH and also formed a hydrogen bond with the histidine ring of His-435. However, the nonsterol ligand was observed in different conformations about the tertiary sulfonamide in the two LXRβ subunits. In one subunit, the T1317 adopted a gauche conformation (Fig. 3a), whereas in the other subunit, it adopted an anti conformation (Fig. 3b). As a result, the nonsterol ligand fits into a position corresponding to the C- and D-rings of eCH and makes weak hydrogen bonds with Ser-278 in each case but did not reach into the volume occupied by the A-ring of eCH and failed to make interactions with either Glu-281 or Arg-319 (Fig. 3, a and b). Despite the differences in the regions of the ligand binding pocket occupied by the eCH and T1317, all of the amino acids contacting both ligands are conserved between LXRα and LXRβ.

**Mechanism of Ligand Activation**—A tryptophan in the LXRα AF2 helix (residue 443) has been shown to be essential for oxyester activation of the receptor (14). In LXRβ, the corresponding residue is Trp-457. In contrast to the published homology model (14), neither the sterol nor nonsterol ligand formed a direct interaction with the AF2 helix in the crystal structure (Figs. 3 and 4). The Trp-457 indole was oriented such that the nitrogen atom was pointed away from eCH, making it
impossible to form a direct hydrogen bond with the epoxide oxygen. Instead, both ligands interacted with His-435, which made an edge to face interaction with the tetrapteron on the inner surface of the AF2 helix (Fig. 4, a and b). The His-435 side chain had some freedom to rotate about its Ca-Cβ bond, allowing it to swing the edge of its imidazole ring across the face of the indole ring. This rotational freedom lets His-435 interact with either the weakly negative π-electron cloud of the five-membered pyrrole ring or the more strongly negative π-electron cloud of the benzene ring (18). This weak electrostatic interaction can become a strongly favorable “cation-π” interaction when the imidazole is positively charged and directed into the most negatively charged regions of the indole π-electron cloud (19, 20).

The hydrogen bonding oxygen atom of the agonist ligand was positioned to donate a hydrogen bond to the epoxide of the sterol side chain at a distance of 3.45–3.50 Å (Fig. 4c). In this orientation, the imidazole directed its electropositive Cα and Ne2 hydrogens toward the Cγ atom and six-membered ring of the tetrapteron side chain, corresponding to the electronegative π-cloud of the indole (18), providing a mechanism for the sterol to hold the AF2 helix in its active conformation (Fig. 4c). The observation that other ligands with only hydrogen bond acceptors in their side chains, such as 24-ketocholesterol and dimethyl cholenamide (7, 14), are also efficacious activators of LXR suggests that this electrostatic interaction is a viable mechanism for ligand activation of the receptor.

In the T1317 structure, the imidazole swung 1.3 Å toward the acidic bis-trifluoromethyl carbinol, bringing the His-435 Ne2 atom to a distance of only 2.59–2.75 Å from the carbinol oxygen (Fig. 4d). In this orientation, the imidazole directed its electropositive Cα hydrogen into the π-cloud of the indole benzene ring, again holding Trp-457 in the active position. The imidazole rotation also opened space for a water molecule, observed in both subunits, that made a hydrogen bond to the backbone Nδ1, further stabilizing the complex. Hydrogen bond lengths tend to correlate with their energy (21), suggesting that the acidic carbinol group makes a stronger hydrogen bonding interaction than the epoxide. This is consistent with quantum mechanics calculations, which indicate that the epoxide oxygen has a relatively weak electrostatic charge as compared with that on the bis-trifluoromethyl carbinol or even as compared with an ordinary hydroxyl group (data not shown). The T1317 hydrogen bond may be further strengthened by partial proton transfer, as can occur when the pKα values of the partners are suitably matched (21). In this case, the bis-trifluoromethyl carbinol group has a pKα of 8.4 in water, relatively close to that of histidine, with a pKα of 6.5–7.0. Thus, the His-Trp interface induced by T1317 may be an example of a cation-π electrostatic interaction (19, 20). Similar cation-π interactions have been observed to regulate the activity of ion channels (22, 23) and enzymes (19, 20). Although the degree of AF2 stabilization by the His-Trp interactions is believed to be different for the sterol and nonsterol ligands, the position of the C-terminal helix does not deviate significantly in the crystalized complexes.

**Mutagenesis of the His-Trp Activation Switch**—To explore the functional differences in the electrostatics of the His-Trp activation switch, we utilized mutants of LXR that might allow activation by T1317 but not eCH. Although tryptophan is the optimal pairing for histidine in a cation-π interaction, phenylalanine or tyrosine can also substitute (18). LXR-GAL4 chime-

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### Table I: Crystallographic data and refinement

| Crystal | LXRβ/T1317 complex | LXRβ/eCH/SRC1 complex |
|---------|-------------------|-----------------------|
| Space group | P2₁2₁2₁ | C222 |
| Unit cell | a = 60.3, b = 82.5, c = 123.2 | a = 71.2, b = 120.0, c = 147.6 |
| Resolution range | 30–2.3 | 20–2.7 |
| Observations (unique) | 308126 (27968) | 141128 (19175) |
| Completeness (final shell) | 95.7 (98.7) | 95.3 (91.6) |
| I/σ (final shell) | 24.8 (3.4) | 28.7 (4.8) |
| Rmerge, % (final shell)* | 5.2 (29) | 5.5 (28) |
| Resolution range | 30–2.3 | 20–2.7 |
| % Rmerge | 7 | 7 |
| Rcryst, % (Rmerge)* | 23.9 (25.7) | 21.5 (27.6) |
| Protein atoms | 3738 | 4124 |
| Ligand atoms | 96 | 58 |
| Water molecules | 320 | 108 |
| r.m.s.d. bonds/angles* | 0.0085/1.675 | 0.014/1.7 |

* Rmerge = Σ I – (I)/Σ I.

* Rcryst = Σ Fobs – Fcalc/Σ Fobs.

* r.m.s.d., root mean squared deviation.
The LXRβ ligand binding pocket. The ligand and amino acid residues forming the ligand binding pocket are shown in stick representation with nitrogen and oxygen atoms colored blue and red, respectively. The ligand is highlighted in bold. Key residues in the binding site are identified by residue number and are also highlighted in bold. a, the LXRβ ligand binding pocket complexed to eCH. b, the LXRβ ligand binding pocket complexed to T1317 showing the gauche conformation of the ligand. c, the LXRβ ligand binding pocket complexed to T1317 showing the anti conformation of the ligand.

Fig. 3. LXRβ ligand binding pocket. The ligand and amino acid residues forming the ligand binding pocket are shown in stick representation with nitrogen and oxygen atoms colored blue and red, respectively. The ligand is highlighted in bold. Key residues in the binding site are identified by residue number and are also highlighted in bold. a, the LXRβ ligand binding pocket complexed to eCH. b, the LXRβ ligand binding pocket complexed to T1317 showing the gauche conformation of the ligand. c, the LXRβ ligand binding pocket complexed to T1317 showing the anti conformation of the ligand.

A Histidine-Tryptophan Switch Regulates LXR

DISCUSSION

The LXRs are important drug targets for the treatment of cardiovascular diseases (24). Nonsterol LXR activators have been shown to increase reverse cholesterol transport (4), decrease local inflammatory markers (25), and prevent atherosclerosis in mice (26). However, the progression of compounds to human clinical trials has been hampered by the effects of LXR agonists on hepatic lipogenesis, which result from increased expression of SREBP-1 (10) and FAS (27). A clear understanding of the molecular basis of small molecule activation of LXR may aid the development of modulator ligands that lack the side effects of potent agonists like T1317.

The structures of the eCH/LXRβ and T1317/LXRβ complexes demonstrate that His-435 is the critical residue in the LBD cloud, weakening the cation-π interaction. This rotation also brought the electropositive Ne2 hydrogen near the electropositive C61 and Ce1 hydrogens of the phenylalanine, further opposing the interaction. Modeling suggested that the W457Y mutant would behave similarly with respect to the cation-π interaction but that the polar hydroxyl of the tyrosine would occupy a lipophilic pocket of LXR, destabilizing the AF2 helix and leading to the inability of either ligand to activate this point mutant.

To rule out the potential influence of the hydrophobic portion of the LXR agonists in these results, a hybrid molecule was synthesized in which the epoxide of eCH was replaced by the bis-trifluoromethyl carbinol of T1317 (Fig. 1a). The T-CH hybrid molecule was assayed for activation of the point mutated LXR-GAL4 chimeras (Fig. 5). Activation was only observed for the W457F LXRα mutant and W457F LXRβ mutant, confirming that the acidic carbinol and not the tertiary sulfonamide in T1317 was responsible for activation of the point mutants.

LXR-GAL4 chimeras were also generated in which His-421 in LXRα or His-435 in LXRβ were mutated to alanine. Neither T1317, eCH, or the T-CH hybrid could activate the H421A LXRα or H435A LXRβ point mutants, confirming the essential role of the histidine in activation of the receptor by both the sterol and nonsterol agonists (Fig. 5).
that mediates ligand activation of the receptor. All of the amino acids that line the ligand binding pocket, including the histidine trigger and the AF2 tryptophan, are conserved in LXRα, so the mechanism of ligand activation is almost certainly identical. Histidine is unique among the naturally occurring amino acids in that it is able to function as either a hydrogen bond donor or acceptor by changing tautomers (28). When bound to eCH, His-435 donated a hydrogen bond to the agonist ligand, whereas it may act as an acceptor when the acidic T1317 is donor or acceptor by changing tautomers (28). When bound to acids in that it is able to function as either a hydrogen bond donor. Reanalysis of the x-ray crystal structures of the eCH and T1317 ligands made contacts with residues in helices 3, 4, 5, the β-turn, helix 10, and indirectly, the AF2 helix and sat in the same common pocket observed for other nuclear receptors. In general, the ligand-receptor interface was dominated by hydrophobic contacts. Although a polar interaction was observed between Glu-281 and the A-ring hydroxyl of the sterol, no corresponding interaction was seen in the T1317 complex, suggesting that it is not required for high affinity binding to LXR. The hydrogen bond to the sterol A-ring hydroxyl by Glu-281, adjacent to Arg-319, is remarkably similar to Arg-Glu pair in the estrogen receptor that binds the phenolic OH of estradiol (17). In each case, the hydroxyl group is bound between an arginine from helix 5 and a glutamate from helix 3. Another important feature of both structures is that the agonist ligands do not fill the LXRβ pocket. Indeed, there was enough room for T1317 to adopt distinct anti and gauche conformations about the tertiary sulfonamide (Fig. 3), suggesting that the LXR pocket can potentially accommodate a wide range of sterol and nonsterol ligands.

In conclusion, the structure of LXRβ in complex with eCH and T1317 identified a His-Trp switch that mediates activation of the nuclear receptor. Sequence alignment indicates that the nuclear bile acid receptor farnesoid X receptor has histidine and tryptophan in corresponding positions, and x-ray crystallography suggests that it also uses a cation-π mechanism of ligand activation (32). No other human nuclear receptors contain a tryptophan in the AF2 helix; however, several receptors have a suitably positioned phenylalanine that could function as a π-donor. Reanalysis of the x-ray crystal structures of the vitamin D receptor (33), thyroid hormone receptor (34), and retinoid-related orphan receptor α (35) shows cation-π stabilization of the AF2 helix through a His-Phe complex. Vitamin D and thyroid hormone directly contact the histidine residue, as seen in the LXR complexes. Since the position and electrostatic properties of the histidine depends on the hydrophob binding character of the ligand (Fig. 4, c and d), it is possible that different classes of ligands could recruit different subsets of coregulators within cells. Although we did not detect differences in the recruitment of SRC1 peptides to LXRα or LXRβ by eCH and T1317 (Fig. 1b), the functional differences in the electrostatic mechanism of AF2 stabilization, combined with the large ligand binding pocket, suggest that LXR and related receptors will be a good targets for the development of modulator ligands with improved therapeutic windows.

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**Fig. 5. Activation of LXR point mutants.** The effect of sterol and nonsterol ligands on the transcriptional activity of LXR histidine and tryptophan mutants as measured by the induction of secreted placental alkaline phosphatase reporter activity on wild type (WT) and point mutant LXR-GAL4 chimeras. Data are expressed as relative reporter activity with the corresponding fold activation as compared with vehicle indicated above the bars. All compounds were tested at 10 μM. All data are n = 3 ± S.E. a, comparison of wild type LXRα point mutants. b, comparison of wild type LXRβ point mutants.
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