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LXR regulation of brain cholesterol: from development to disease

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Abstract

Liver X Receptors (LXRs) are master regulators of cholesterol homeostasis and inflammation in the central nervous system (CNS). The brain, which contains a disproportionately large amount of the body's total cholesterol (~25%), requires a complex and delicately balanced cholesterol metabolism to maintain neuronal function. Dysregulation of cholesterol metabolism has been implicated in a number of neurodegenerative diseases including Alzheimer's (AD), Parkinson's (PD), and Huntington's (HD) diseases, among others. Due to their cholesterol sensing and anti-inflammatory activities, LXRs are positioned centrally in the everyday maintenance of central nervous system function. This review will focus on recent research into the role of LXRs in the CNS during normal development and homeostasis and in disease states.

Keywords

Liver X Receptor; cholesterol; lipoprotein; brain; neurodegenerative disease

LXRS: adopted orphans turned masters of cholesterol metabolism

LXRs were originally identified as “orphan” nuclear receptors of the type II superfamily, a group that comprises non-steroid nuclear receptors that form obligate heterodimers with the Retinoid X Receptors (RXRs). LXRs, together with peroxisome proliferator activated receptors (PPARs), are the predominant type II nuclear receptors that regulate lipid homeostasis in the brain [1]. The LXR family includes two isoforms: LXRα is prominently expressed in the liver and other tissues critical for peripheral lipid metabolism such as the kidney, small intestine, spleen, and adipose tissue, whereas LXRβ is more broadly expressed, but is found most prominently in the liver and the brain. LXRs form obligate heterodimers with all RXR isoforms (α, β, or γ) that recognize and bind to sequence-specific binding elements within the promoters and enhancers of target genes, and initiate transcription. In macrophages, DNA binding by LXRs is largely dependent on enhancer priming, where occupancy of an enhancer region by the lineage-determining transcription factor PU.1 allows chromatin remodeling to make LXR recognition sequences accessible for

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binding [2]. It is likely that LXRs collaborate with a diverse group of lineage-determining factors in other cell types, providing tissue- and cell type-specific regulation of LXR signaling, although the influence of enhancer priming on LXR signaling remains largely unexplored.

LXR:RXR heterodimers associate with DNA in the nucleus regardless of their ligand binding status. When unbound to ligand, LXRs mediate transcriptional repression by interacting with corepressors such as nuclear receptor co-repressor (NCoR) or silencing mediator for retinoid and thyroid receptors (SMRT) and histone deacetylase 3 (HDAC3) [1], functionally silencing the expression of target genes (Fig 1A). In the presence of ligand, the co-repressor complex is exchanged for a co-activator complex, thereby promoting transcription (Fig 1B). Additionally, ligand activated LXRs have a transrepressive activity whereby they can become SUMOylated and interact with co-repressor complexes on AP-1 and NFκB target genes, repressing transcription of pro-inflammatory genes (Fig 1C, [3]).

LXRs are key regulators of transcriptional programs for both cholesterol homeostasis and inflammation in the brain, and disruptions of LXR signaling can be observed in many neurodegenerative diseases. This review focuses on recent advances in our understanding of the role of LXRs in cholesterol homeostasis in the brain, especially new roles discovered for LXR brain development. Additionally, we explore evidence linking LXR signaling to neurodegenerative diseases, including Alzheimer's (AD), Parkinson's (PD), and Huntington's (HD) diseases.

Cholesterol homeostasis in the CNS

In the CNS, cholesterol is synthesized locally and brain cholesterol metabolism is largely separated from peripheral cholesterol metabolism by the blood brain barrier (BBB). Cholesterol synthesis and clearance are highly regulated to create a tightly coupled homeostatic system allowing for a modest amount of cholesterol turnover while keeping overall levels constant (this process has been comprehensively reviewed recently by Vitali et al. [4]). During development, especially during myelinogenesis, both astrocytes and neurons produce cholesterol prolifically, however neurons downregulate expression of many genes involved in the cholesterol synthesis machinery as the brain matures [4]. Adult neurons rely on their ability to take up cholesterol synthesized by neighboring glial cells in order to maintain membrane plasticity and cellular function. In the brain, cholesterol is transported as a component of high density lipoprotein (HDL)-like particles which are similar to peripheral HDLs in their ability to both acquire and discharge cholesterol and phospholipid cargo. The major apolipoprotein component of these particles in the CNS is apolipoprotein E (apoE), which mainly mediates the transport of lipids between astrocytes and neurons or oligodendrocytes in a process termed reverse cholesterol transport (RCT). LXRs directly regulate the transcription of apoE and its lipidating transporters ABCA1 and ABCG1. In addition to regulating cholesterol efflux via RCT, LXRs also regulate the uptake of cholesterol by members of the low density lipoprotein receptor (LDLR) family of cell surface receptors [5].

In keeping with the role of LXRs as modulators of cholesterol homeostasis, cholesterol derivatives such as oxysterols and cholestenoic acid act as ligands for LXR. CNS oxysterols involved in LXR modulation include 24(S)-hydroxycholesterol (24-OHC), 22(R)-hydroxycholesterol, 24(S),25-epoxycholesterol, and 27-hydroxycholesterol (27-OHC) [6]. 24-OHC, the most abundant oxysterol in the brain, is generated by hydroxylation of cholesterol in neurons by the cytochrome P450 enzyme cholesterol 24-hydroxylase (CYP46A1) and the hydroxylated cholesterol species are normally then cleared from neurons, possibly in an ABCA1 dependent manner [7]. 24-OHC subsequently crosses the BBB largely by passive diffusion across membranes [8], and this clearance represents the major pathway of cholesterol efflux from the brain. 24-OHC also acts as either a pro-survival or pro-death factor in neurons. At physiological concentrations 24-OHC induces LXR signaling in neurons and generates a neuroprotective response [9,10], while at high concentrations 24-OHC inhibits LXR transcriptional activity [10], promoting a “necroptosis-like” death pathway in neurons [11,12]. Recently it has been proposed that the neuroprotective action of 24-OHC involves allosteric modulation of N-methyl-D-aspartate receptor (NMDAR) function, but this activity is the result of direct binding to NMDA receptors and not LXR activation [13,14], adding further complexity to the mechanisms by which LXR-activating oxysterols act on neurons.

In contrast to 24-OHC, 27-OHC is synthesized at high levels by a variety of peripheral cells and crosses the BBB to enter the brain [4], allowing 27-OHC to act as an indicator to the brain of plasma cholesterol levels. Decreased levels of 27-OHC have been observed in several neurodegenerative disorders including AD, HD, and PD [15]. 27-OHC may link high peripheral cholesterol with many CNS diseases through its ability to upregulate the brain renin-angiotensin system in an LXR-dependent manner [16]. Additionally, Zhang et al. recently showed that peripheral injection of 27-OHC into rats upregulates LXRα and ATP-binding cassette transporter ABCA1 in the brain, downregulates HMG Co-A Reductase and LDLR, and produces dose-dependent impairments of spatial memory performance in the Morris Water Maze (MWM) task [17]. Heverin et al. also report that Cyp27 deficient mice, which lack the enzyme necessary for 27-OHC production, do not experience the negative effects of high cholesterol diet on MWM performance and hippocampal Arc expression that their wild type littermates exhibit [18]. Interestingly, 27-OHC may also play a complicated role in AD pathology, as 27-OHC treatments have been observed to upregulate amyloid beta (Aβ) production in neuronal cell lines [19,20] but downregulate Aβ production, potentially in an LXR-mediated manner, in primary human neurons [21].

Oxysterols such as 24-OHC and 27-OHC also act as ligands of LXR to facilitate transcription of a battery of genes involved in cholesterol efflux, or RCT. The formation and transport of lipoproteins in the CNS has been of intense interest for over a decade, since expression of variants of the major apolipoprotein produced in the brain, apoE, was found to be the dominant non-familial risk factor for AD [22]. However, the process by which nascent apolipoproteins are formed in the brain remains poorly understood. Astrocytes are the main producers of lipoproteins in the brain, although microglia also produce lipoproteins to a lesser extent. Unlipidated or lipid-poor apoE interacts with ABCA1, which is expressed throughout the brain, and ABCA1 mediates the transfer of cholesterol and phospholipids onto apoE. ApoE thus acts to scaffold the formation of HDL-like particles that are secreted

into the interstitial fluid by astrocytes. Other lipid transporters such as ABCG1 are more restricted both in their expression patterns and ability to transfer cholesterol onto apoE-containing particles. LXR, as a direct transcriptional regulator of apoE, ABCA1, and ABCG1, responds to the generation of oxysterols as a result of excess cholesterol levels by upregulating the RCT machinery in cells, acting as a master integrator for lipid homeostasis within the brain (Fig 2, [4]).

Lipoprotein receptor regulation

Cholesterol homeostasis in the brain not only involves the production and efflux of cholesterol from cells but also its cellular uptake via lipoprotein receptors. This family of receptors is expressed ubiquitously in the brain, and includes LDLR, the very low-density lipoprotein receptor (VLDLR), apolipoprotein E receptor 2 (apoER2), and LDLR-related protein 1 (LRP1). For an excellent review of lipoprotein receptors in the CNS, especially as implicated in disease states, see Lane-Donovan et al. [23].

Activation of LXRs downregulates lipoprotein receptor cell surface expression and therefore cholesterol uptake, promoting its cellular efflux. This occurs via an indirect mechanism in which LXRs mediate transcriptional induction of inducible degrader of LDLR (IDOL). IDOL is an E3 ubiquitin ligase that specifically targets LDLR [24,25] for epsin-mediated endocytosis [26] and subsequent degradation. IDOL also ubiquitylates VLDLR and ApoER2, but not the related lipoprotein receptor LRP1 [27]. This mechanism has been shown to be regulated in a tissue- and species-dependent manner [28]. In cultured cells, it was determined that LXR activation increased IDOL transcript and protein and reduced VLDLR protein levels, implying a potential role for IDOL in development by regulating the ability of neuronal guidance cue Reelin to signal through its receptor VLDLR [27,29].

However, it was not clear until recently that an LXR-IDOL axis was relevant in the brain. Importantly, knockout of IDOL in mice expressing human mutations for amyloid precursor protein (APP) and presenilin 1 (PS1), which normally develop amyloidosis and inflammation characteristic of AD, decreased levels of soluble and insoluble levels of Aβ as well as inflammation [30]. The IDOL KO appeared to facilitate microglial clearance of Aβ, likely through permitting increased expression of LDLR that can act as a receptor for apoE, Aβ, or complexed apoE/Aβ species [30]. Recently a deubiquitylase, ubiquitin-specific protease 2 (USP2), has been reported to interact with IDOL and promote its deubiquitylation, which both stabilizes IDOL and decreases its ability to ubiquitylate the LDLR [31,32]. While USP2 expression did not appear to respond to LXR ligands, the participation of this protein indicates that the LXR-IDOL-LDLR pathway is part of a much larger and complex metabolic regulatory circuit that remains to be fully identified.

A role for LXRs in CNS development

In recent years, LXRs have been described to have widely varying roles in the regulation of CNS development, including migration of cortical neurons to the superficial cortical layers [33], migration of granule neurons in the cerebellum [34], and regulation of lipid metabolism in the developing retina and lens of zebrafish [35]. LXRα/β knockout animals

were found to have pathological changes in the substantia nigra, globus pallidus, and subthalamic nucleus that included lipid accumulation and neurodegeneration [36], and LXRβ knockout mice exhibit progressive loss of motor neurons in the spinal cord [37] and increased sensitivity of substantia nigra dopaminergic neurons to cholesterol depletion [38]. Some of the diverse roles proposed for LXRs in different brain regions are highlighted in Fig 3.

In 2009, Sacchetti et al. reported that LXR signaling in the ventral midbrain (VM) during development is essential for the generation of dopaminergic neurons, and that overexpression of LXRβ or application of LXR ligand 22-HC increases the rate of dopaminergic differentiation of embryonic stem cells [39]. The major endogenous ligands for LXR in the murine midbrain were found to be cholic acid and 24(S),25-epoxycholesterol (24,25-EC), which promote neurogenesis and survival of red nucleus neurons and regulate dopaminergic neurogenesis, respectively [40]. Other endogenous LXR ligands, a subset of cholestenoic acids, have been identified to activate LXR selectively in motor neuron populations. Interestingly, the effects of these ligands vary widely, with 3β,7α-diHCA acting neuroprotectively in cultured oculomotor neurons, 3βH,7O-CA having no effect on neuronal survival, and 3β,7β-diHCA and 3β-HCA inducing cell death [41]. It has been suggested that cholestenoic acids compete for activation of LXR in motor neurons, and that the relative ratios of various cholestenoic acids in CSF could provide important information about the disease state of patients with progressive motor neuronopathies and indicate potential therapeutic targets.

LXR cholesterol regulation participates in myelination

The majority of the cholesterol in the brain is contained in myelin [4], implying that regulators of cholesterol metabolism such as LXR have critical roles in oligodendrocytes. LXR knockout mice have reduced myelination in the cerebellum and sciatic nerve, coincident with motor deficits, and LXR activation by the synthetic ligand TO901317 increased expression of myelin-related genes [42,43]. Indeed, loss of LXRβ particularly was found to result in impaired locomotion and decreased myelination in the corpus callosum and optic nerve, and this coincided with a reduction in the differentiation of radial glial cells (RGCs) into oligodendrocyte progenitor cells (OPCs) during development [44]. It has also been observed *in vitro* that primary oligodendrocytes increase LXRβ expression during differentiation [45], and that the LXR agonist TO901317 stimulates oligodendrocyte differentiation [43], induces LXR target gene expression and mediates cholesterol efflux from oligodendrocytes [45]. TO901317 was also able to stimulate remyelination in organotypic slice cultures that had experienced demyelinating lesions [43], although another study reported no remyelinating effect of TO901317 treatment on cuprizone-induced lesions in vivo [46]. There is evidence that crosstalk between LXRs and the Wnt/β-catenin pathway might add to the effect of LXRs on myelin-related gene expression [42] in a context dependent manner, by inhibiting myelin gene expression in peripheral Schwann cells but not oligodendrocytes [47].

LXRs in water transport and CSF production

LXRβ knockout mice have decreased peripheral expression of the major water channel aquaporin-1, specifically in the pancreas [48] and kidney [49], resulting in insufficient excretion of pancreatic enzymes and dysfunctional regulation of urine volume and osmolarity. Wang et al. reported in 2002 that LXRα/β KO mice exhibit morphological changes in the choroid plexus, the organ responsible for CSF secretion, indicating that LXRs might also play a role in regulating water transport in the brain. In fact, one of the most striking phenotypes in LXRα/β KO mice was the occlusion of the lateral ventricles with age, with the lateral and third ventricles closing completely by 1 year of age [36]. In a 2015 study, Dai et al. followed up on this finding to report that LXRα and β are expressed in the choroid plexus and in ependymal cells, and that several genes involved in structural integrity as well as aquaporin 1 and carbonic anhydrase IX are downregulated at the choroid plexus in LXRα/β KO mice. Interestingly, they also report an increase in aquaporin 4 in astrocytic end feet in the LXRα/β KO mouse, indicating that LXRs have broad effects on CSF production and clearance [50].

Anti-inflammatory effects of LXRs

Although LXRs have established roles in mediating inflammatory functions in macrophages, B cells, T cells, and dendritic cells [51], the pathways and ligands involved in LXR inflammatory regulation are poorly understood. The role of microglia in brain cholesterol transport is unclear, as microglia are a minor contributor to the pool of lipidated apoE particles, which are postulated to have anti-inflammatory effects. The integration of lipid and inflammatory signaling in microglia is critical to CNS function, as microglia accumulate lipids during synaptic pruning and the phagocytosis of apoptotic cells [52]. Reducing microglial cholesterol levels in cultured cells has been shown to inhibit phagocytic capability [53,54] but also facilitates lysosomal trafficking and the intracellular degradation of Aβ [55], underscoring the importance of microglial lipid regulation in disease states.

LXRs also have an established role in regulating the inflammatory phenotype of peripheral macrophages, both through their transrepressive activity and their transcriptional activation of genes that modify phagocytic capability and response to stimuli [51]. Recently, it has been shown that LXRs exhibit similar transrepressive activities in microglia [3] and regulate activity of microglial phagocytic receptors such as the tyrosine kinase MerTK [56,57], although the role of inflammatory regulation by LXRs in microglia remains to be fully elucidated. It has been proposed that the anti-inflammatory activities of LXRs influence their therapeutic potential for several CNS disorders, which will be specifically addressed below.

LXRs in CNS Disorders

LXRs have been implicated in the regulation of a wide array of brain processes and dysfunction: anxiety, through the regulation of GABA synthesis [58]; neuroprotection against ethanol exposure during cerebellar development [59]; and recovery after traumatic brain injury, possibly through apoE-dependent effects on axonal preservation [60] are a few

processes that LXRs modulate. LXRs also have been ascribed neuroprotective roles in stroke models [61,62] and implicated in ALS, as it is well-documented that LXRβ knockout mice exhibit progressive loss of motor neurons in the spinal cord, resulting in motor deficits by 8 months of age [37,38,63]. Here we describe in detail a few of the CNS neurodegenerative diseases in which LXR function has been recently investigated.

Alzheimer's disease

AD is a progressive neurodegenerative disorder associated with profound memory loss and neuroinflammation and pathologically characterized by the accumulation of both soluble and deposited forms of amyloid β. LXRs have been a focus of study in Alzheimer's research since the E4 variant of LXR target gene ApoE was first reported to be the major risk factor for non-inherited forms of AD [1]. Genetic inactivation of LXRs and ABCA1 in AD mouse models results in exacerbated Aβ deposition [64,65], possibly due to reductions in microglial phagocytosis [66], but treatments of AD mouse models with LXR agonists have produced widely varying results on pathology. While some studies report that LXR agonists effectively increase Aβ clearance in AD models and reduce plaque load, others report no change in Aβ pathology (reviewed by Skerrett et al. [1]). The reasons for the varying success of LXR agonists on Aβ pathology remain unknown. Importantly, LXR agonists are consistently reported to mediate cognitive improvements in AD mouse models, with all nine studies that addressed behavior reporting improvements across a range of mouse models and treatment paradigms [1]. The positive effects of LXR agonists in AD mouse models are commonly attributed to increased expression and lipidation of apoE. In addition to its role in cholesterol homeostasis, by which it promotes synaptic function and maintenance, ApoE is known to interact with Aβ and can facilitate its uptake and degradation by microglia and its transport across the BBB to the periphery. However, it has also been established that LXRs have an important regulatory role in microglia through the transrepression of pro-inflammatory genes and by regulating microglial activity.

Recently it has been reported that LXRs might be able to affect neuronal survival in an AD context, in a neuron-intrinsic manner. Previous evidence has suggested that RXR and its heterodimer partners are able to regulate the transcription of neuronal genes important for neurogenesis and neurite extension [67–70], synaptic function [71], and neuronal survival [1]. A recent study from Sandoval-Hernandez et al. reports that treatment of 3xTg-AD mice with LXR agonist GW3965 increases proliferation of neural precursors in the subgranular zone and rescues Aβ-induced deficits in long-term potentiation (LTP) in a protein-synthesis dependent manner [72]. In a later study, Sandoval-Hernandez et al. determined that GW3965 treatment was able to effect improved performance on cognitive tests in aged 3xTg-AD mice coincident with reduced DNA methylation in the hippocampus [73]. Reduced DNA methylation was especially observed at genes involved in synaptic function and neurogenesis. Additionally, LXR agonist TO901317 abrogated the loss of cholinergic neurons in APP/PS1 mice [74]. Together, this body of evidence indicates that LXR may play a neuroprotective role in the context of AD, and that the mechanism by which LXR is neuroprotective may not be directly related to its functions in cholesterol homeostasis.

Parkinson's disease

PD is characterized by neurodegeneration of dopaminergic neurons in the midbrain, which results in motor deficits including tremor, bradykinesia, muscle stiffness, and changes in posture and motion. The role of LXRs in midbrain neurogenesis suggests that they may play an important role in the pathogenesis of PD. PD is prominently associated with degeneration of dopamine neurons in the substantia nigra, and these neurons also undergo degeneration in LXRα/β KO mice [36]. Additionally, LXRβ-KO mice have increased sensitivity to challenge with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [75] or β-sitosterol [38], exhibiting increased death of substantia nigra neurons in response to treatment. The LXR agonist GW3965 was neuroprotective in MPTP treated mice [75], suggesting a potential therapeutic role for LXR agonists in PD treatment. However, it remains unclear to what extent this neuroprotection by LXRs might be due to either neuron intrinsic actions or anti-inflammatory activity in microglia or astrocytes, since PD is associated with a strong neuroinflammatory response. Further complicating the role of LXRs in PD, LXR agonists have been observed to induce transcription of α-synuclein in cultured cell lines, and this protein is frequently found to be deposited in neurons in PD patients [76,77]. Further exploration is needed to elucidate the complex mechanisms by which LXRs affect PD pathogenesis.

Huntington's disease

HD results from an autosomal dominant mutation in the *HTT* gene that results in a mutant huntingtin protein. This mutation prominently affects the nervous system, causing early onset (usually by age 50) neurodegeneration together with a host of motor problems, such as chorea and dystonia, and cognitive abnormalities. Both mouse models and human patients with HD exhibit defects in cholesterol homeostasis, with decreased levels of CYP46A1 implicated in both HD patients and the R6/2 Huntington's mouse model [78]. Knockdown of CYP46A1 in the mouse striatum reproduces HD-like striatal neuron degeneration and rotarod deficits while overexpression of CYP46A1 in the striatum of R6/2 mice reduces the severity of cell loss and HTT aggregates and improve motor function [79]. It is unclear if this mechanism involves CYP46A1-dependent production of 24-OHC and the subsequent activation of LXRs, however, substantial overproduction of 24-OHC in a CYP46 overexpressing mouse was unable to effect LXR activation in the brain or liver [80]. Additionally, CYP46A1 knockout mice do not exhibit a neurodegenerative phenotype although they do have severe deficits in contextual learning that correlated with LTP deficits [81]. It has also been suggested that wild-type huntingtin, but not the mutant forms, can directly interact with LXR and participate in target gene regulation [82].

Concluding Remarks

While agonism of LXRs has therapeutic potential in these diseases of CNS function and others, targeting LXR remains problematic. In experimental models, synthetic LXR ligands increase plasma cholesterol levels and cause hypertriglyceridemia [83]. New compounds with better tissue specificity or LXR isoform targeting could allow for better translatability of LXR agonists, and elucidation of the mechanisms by which LXRs modulate neuronal survival and neuroinflammation can further inform the search for targeted drugs.

Additionally, the recent discovery of several new cholesterol derivatives that function as LXR agonists has exposed exciting novel roles for LXRs in the development of midbrain neurons. The elucidation of LXRs' endogenous ligand repertoire will further our understanding of how this receptor regulates lipid metabolism as conditions in the brain change during development and aging. LXRs remain promising therapeutic targets in a number of areas, and their position at the intersection between cholesterol homeostasis and the regulation of inflammation makes them a key regulator of brain function in both normal development and aging and in disease states.

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Outstanding Questions Box

- How is the cell type specificity of LXR activation regulated in the CNS? LXRs respond to a large variety of ligands with a wide range of transcriptional effects, and it's likely that their DNA binding ability is modulated by cooperation with other lineage-determining transcription factors.
- Can we identify the repertoire of LXR ligands brain-wide over the course of development and aging? Spatial and temporal regulation of specific cholesterol derivatives in the midbrain has been linked to the ability of LXRs to regulate neurogenesis. As endogenous ligands can elicit diverse responses in LXR signaling, it will be important to profile the cholesterol milieu while studying LXR activity.
- What is the role of LXRs in different neuronal populations? LXRs have been implicated in neurogenesis or neuronal survival of several subtypes of neurons, and it will be important to study if they have cell type-specific transcriptomes as well as broad neuroprotective activities.
- How do perturbations in cholesterol metabolism during disease states influence LXR signaling? Changes in the levels of cholesterol derivatives in both plasma and CSF have been observed in several neurodegenerative diseases, but the mechanisms behind these perturbations and their effects on LXR signaling require further study.

Trends Box

- Liver X Receptors (LXRs) are master regulators of cholesterol and inflammation, are critical for brain homeostasis, and are implicated in several neurodegenerative diseases.
- Due to the complexity of metabolic regulation by LXRs, it has been difficult to define their roles in normal function or disease states. LXRβ is expressed ubiquitously in the CNS and performs important functions across many cell types.
- Emerging research into endogenous LXR ligands, which are mainly oxysterols, has determined new roles for these receptors in CNS development and maintenance.
- Further exploration of the action of endogenous LXR ligands will better inform our understanding of its function in development and homeostasis, and provide insight into the role of LXR in disease states.

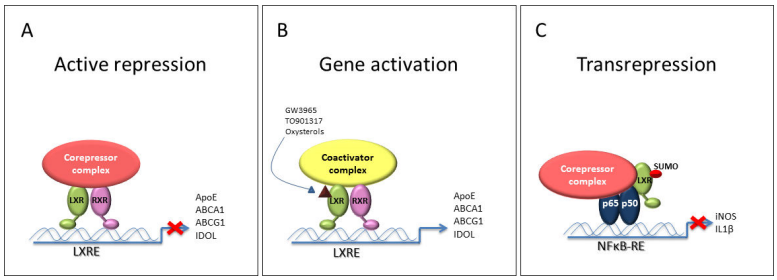

Figure 1. Mechanisms of transcriptional regulation by LXRs

(A) In the absence of ligand, LXR:RXR complexes bind DNA at LXR response elements, where they interact with co-repressor complexes containing NCoR or SMRT and HDAC3. (B) In the presence of synthetic or endogenous ligands, LXRs undergo a conformational change that dissociates the co-repressor complex, allowing recruitment of a co-activator complex and the promotion of target gene transcription. (C) Ligand-bound LXR can also be SUMOylated, which promotes its localization to NFκB or AP1 response elements where it stabilizes the interaction between these transcription factors and their co-repressor complexes, thereby inhibiting the expression of pro-inflammatory genes.

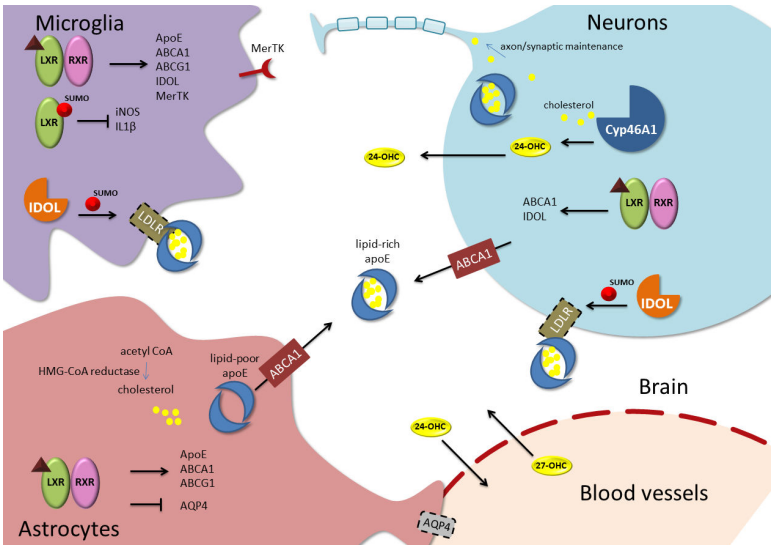

Figure 2, Key Figure. Cell type-specific roles of cholesterol metabolism and LXR signaling in the CNS

Bottom left, astrocytes are the major producers of cholesterol in the CNS, and HMG-CoA reductase mediates conversion of acetyl CoA to cholesterol. ApoE, the major protein constituent of the HDL-like complexes that transport cholesterol from astrocytes throughout the CNS, is transcriptionally regulated by LXR along with its lipidating transporters ABCA1 and ABCG1. Nascent apoE is packaged with cholesterol and other lipid species by ABCA1 and released from the cell as HDL-like particles. Additionally, LXRs inhibit astrocytic expression of AQP4 and therefore participate in regulation of water transport at the BBB. Bottom right, oxysterols but not cholesterol may cross the BBB. The exchange of CNS-synthesized 24-OHC and peripherally synthesized 27-OHC allows communication between brain and periphery regarding cholesterol metabolism. Upper right, neurons use cholesterol for maintenance of axons and synapses, which is required for their proper function. Adult neurons rely on cholesterol delivery by astrocyte-synthesized apoE, which is recognized and endocytosed by members of the LDLR family. In conditions of excess cholesterol, neuronal Cyp46A1 converts cholesterol to 24-OHC, which can diffuse through the membrane and also acts as a ligand for LXR. In neurons, LXR activation lowers intracellular cholesterol by promoting transcription of ABCA1, which loads cholesterol onto apoE. Additionally, the E3 ubiquitin ligase IDOL mediates the SUMOylation of LDLR family members, leading to their endocytosis and degradation and therefore decreased cellular uptake of lipids. Upper left, microglia, like astrocytes, produce and lipidate apoE in an LXR-dependent manner. As in neurons, LXRs in microglia transcriptionally regulate IDOL and therefore surface expression of LDLRs. Additionally, in microglia LXRs regulate expression of phagocytic genes such as MerTK, and SUMOylated LXRs mediate transrepression at pro-inflammatory promoters.

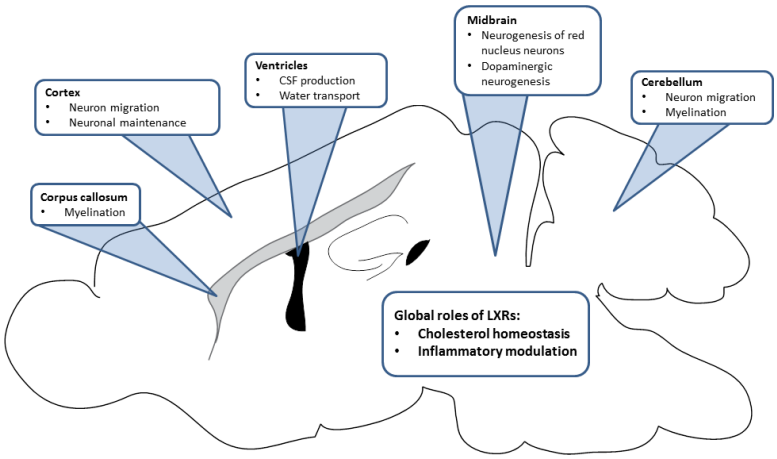

Figure 3. Region-specific roles for LXR signaling in development and homeostasis

Global roles of LXRs in the brain include regulation of cholesterol homeostasis and inflammation. LXRs have also been implicated in myelination, especially in the corpus callosum and cerebellum, and are important regulators of CSF production in the ventricles and water transport at the BBB. LXRs also have important roles in neuronal function, and have been observed to regulate neurogenesis of red nucleus neurons and dopaminergic neurons in the midbrain as well as neuron migration in the cortex and cerebellum.

TABLE 1

Central actions of LXR ligands

Ligand	Name	Effect	Neurodegenerative diseases	REF
Natural	hydroxycholesterol	- Neuroprotective at low concentrations - Necro-apoptotic at high concentrations - Stimulates RCT gene transcription	- Low in HD - Increased early in AD, decreased at late stages	[9-12]
	22(R)-hydroxycholesterol	- Stimulates dopaminergic differentiation of embryonic stem cells		[39]
	27-hydroxycholesterol	- Upregulates brain renin-angiotensin system - Downregulates HMG Co-A Reductase and LDL - Linked to impaired spatial memory performance - Stimulates RCT gene transcription	- Low in AD, HD, and PD	[15-17]
	Cholic acid	- Promotes neurogenesis and survival of red nucleus neurons		[40]
	24(S),25-epoxycholesterol	- Regulates dopaminergic neurogenesis		[40]
	Cholestenoic acids	- Can be neuroprotective or induce death depending on ligand - Specifically act on motor neurons		[41]
Synthetic	TO901317	- Modifies expression of myelin-related genes - Stimulates oligodendrocyte differentiation - Increased expression of RCT-related genes	- Improves survival of cholinergic neurons in an AD mouse model - Anti-inflammatory	[42,43,45,47,74]
	GW3965	- Increased expression of RCT-related genes	- Improves behavioral performance in AD mouse models - Rescues Aβ-induced deficits in LTP - Neuroprotective in PD models - Anti-inflammatory	[1,72,73,75]