

Therapeutic potential of liver X receptor beta in depression and anxiety

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Liver X receptors (LXRs), particularly LXR β , are emerging as crucial players in the translation of basic neuroscience to clinical psychiatry. These nuclear receptor transcription factors, initially known for their roles in cholesterol metabolism and inflammation, are now revealing promising connections between molecular mechanisms and psychiatric symptoms. This review highlights recent breakthroughs in understanding LXR β 's regulation and function in behaviors relevant to depression and anxiety, derived from studies using animal paradigms that capture specific features of these disorders. We explore how these preclinical findings are shaping our comprehension of mood-related behaviors at the molecular level and potentially paving the way for innovative therapeutic strategies. As a ligand-activated transcription factor, LXR β represents a novel target for drug development, potentially bridging the gap between bench discoveries and bedside treatments for neuropsychiatric disorders. We discuss the challenges and opportunities in translating LXR β research into clinical interventions, emphasizing the potential for personalized medicine approaches in psychiatry. This bench-to-bedside article underscores the importance of LXR β research in advancing our understanding and treatment of complex mental health conditions, while acknowledging the nuanced interpretation required when extrapolating from animal studies to human disorders.

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Historical Perspective: LXR β

Liver X receptors, LXR α and LXR β , are members of the nuclear receptor family of ligand-activated transcription factors (1). The first cloned member, initially named RLD1 and liver X receptor (2, 3), was later renamed LXR α . Our laboratory discovered LXR β , originally calling it OR-1 (4). Other labs simultaneously identified it under various names: UR (5), NER (6), and RIP-15 (7). Its similarity to LXR α led to its current name, LXR β .

LXR α is well-known for its role in cholesterol homeostasis, with both receptors often dubbed master regulators of this process (8, 9). Oxysterols, which are oxygenated forms of cholesterol, serve as natural ligands for LXRs. While LXRs are most recognized for their influence on cholesterol homeostasis, LXR β 's functions extend far beyond. It regulates various transport mechanisms, including aquaporins for water transport (10–12), GLUT4 for glucose transport (13), MCT8 and MCT10 for thyroid hormone transport (14), and ApoE and ABC transporters for cholesterol transport (15). This diverse involvement explains LXR β 's wide-ranging effects throughout the body.

Research on LXR α has primarily focused on organs involved in lipid metabolism, such as the liver, intestine, adipose tissue, and within the immune system, particularly in macrophages (16). In contrast, LXR β shows a broader tissue distribution. While its liver expression is minimal, LXR β is well-expressed in immune system cells, CNS glial cells, the colon, gallbladder, pancreatic islets, retina, and inner ear (17–23). It is also widely expressed in fetal brain neurons (24, 25). Both LXR α and LXR β are present in reproductive tissues like the ovary, testis, prostate epithelium, and epididymus, where they play significant roles (26–29).

LXRs form heterodimers with retinoid X receptors (RXRs) and bind to specific DNA response elements called DR4s. These are direct repeats of the half-site sequence 5'-G/AGGTCA-3', separated by four nucleotides, also used by thyroid hormone receptors (3). Our research has shown that LXR β protects neurons in both central and peripheral nervous systems. This protection extends to dopaminergic neurons in the substantia nigra (30), large motor neurons in the spinal cord's ventral horn (31, 32), epithelial cells of the choroid plexus (11), retinal ganglion cells (22), and spiral ganglion neurons (23). Recent reviews have thoroughly explored

LXRs' role in neurodegenerative diseases like Alzheimer's disease (AD) (8, 33), Parkinson's disease (PD) (34, 35), amyotrophic lateral sclerosis (ALS) (36), and multiple sclerosis (MS) (37).

Role of LXR β in Depression

Studies have demonstrated LXR β 's protective effects against depression-like behaviors in rodents, influencing neurons, microglia, oligodendrocytes, and astrocytes (Table 1). In rats exposed to chronic unpredictable stress (CUS), hippocampal LXR β levels decrease. Treatment with the LXR agonist GW3965 reduces depression-like behavior and improves hippocampal neurogenesis in these rats (38). LXR's inhibition of microglial activation and neuroinflammation is a crucial protective mechanism, as seen in various injury paradigms (39–43). Several studies show that GW3965 treatment can modulate microglial status and suppress neuroinflammation, thereby improving emotional and cognitive functions as well as reducing depression-like behaviors in CUS-induced and other experimental paradigms (44–47). Additionally, GW3965's stimulation of oligodendrocyte maturation and enhanced myelination may contribute to the antidepressant effects of LXR agonists (48).

While LXR's role in depression-like behaviors has been extensively studied in mice (Table 1), research on LXR in the human brain is limited. Only one study to date has explored this connection (49), identifying a link between impaired LXR signaling and schizophrenia. RNA sequencing of dysfunctional dorsolateral prefrontal cortex gray matter revealed gene expression patterns indicative of abnormalities in LXR-regulated lipid metabolism pathways in schizophrenia patients. The study concluded that aberrations in LXR/RXR-regulated lipid metabolism lead to decreased lipid content in the prefrontal cortex, correlating with reduced cognitive performance.

Role of LXR β in Anxiety

Anxiety disorders are the most prevalent psychiatric conditions (50). Female mice lacking LXR β exhibit anxiety-like behavior and impaired behavioral responses (Table 1) (51). These mice show reduced expression of glutamate decarboxylase (65+67), the enzyme responsible for GABA

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**Table 1.** Summary of LXR β effects on depression-like and anxiety-like behaviors in experimental rodent paradigms

Neuropsychiatric-related behaviors	Experimental paradigm	LXR β ligand	Effects	Reference
Depression-like	Chronic unpredictable stress (CUS) exposure in rats	GW3965	Regulation of hippocampal neurogenesis	(38)
	CUS and lipopolysaccharide exposure in mice	GW3965	Inhibits microglial M1 polarization and restores synaptic plasticity	(44)
	CUS exposure in mice	GW3965	Suppresses microglial activation and neuroinflammation in hippocampal subregions	(45)
	CUS exposure in mice	GW3965	Improvement of oligodendrocyte maturation and enhancement of myelination	(48)
	CUMS and corticosterone drinking paradigm in mice	T0901317	Suppresses neuroinflammation by inhibiting NF- κ B signaling and NLRP3 inflammasome activation	(46)
Anxiety-like	LXR β -deficient female mice	–	Decreased glutamic acid decarboxylase (65+67) in the ventromedial PFC	(51)
	LXR β -deficient male mice	–	Abnormality in locomotor activity and exploratory behavior, demyelination	(52)
	Forced swimming stress exposure in mice	GW3965	Rebalancing excitatory and inhibitory neurotransmission	(54)
	Astrocyte-specific LXR β -deficient mice	–	Impaired synaptic transmission in mPFC	(53)

synthesis, in the ventromedial prefrontal cortex (PFC). Further studies demonstrated that loss of LXR β function results in abnormalities in locomotor activity and exploratory behavior, as well as anxiety-like symptoms (52). LXR is expressed in microglia, astrocytes, and oligodendrocytes in the adult mouse CNS (18). Intriguingly, specific deletion of LXR β from astrocytes resulted in anxiety-like, but not depression-like behaviors in adult male mice (53). This work suggests that astrocytic LXR β in the medial PFC plays a critical role in regulating synaptic transmission. In an experimental paradigm of stress-induced anxiety-like behavior, the LXR agonist GW3965 exerted anxiolytic effects by restoring the balance between excitatory and inhibitory neurotransmission through LXR β signaling activation in the amygdala (54).

Role of LXR β in Autism

Autism, now referred to as autism spectrum disorder (ASD), is a pervasive neurodevelopmental disorder. Defects in dentate gyrus neurogenesis appear to be implicated in the development of ASD-like behaviors. LXR β -deficient mice exhibited early alterations in dentate gyrus neurogenesis and displayed autistic-like behaviors, such as deficits in social interaction and repetitive behaviors (55). Additionally, LXR agonist T0901317 attenuated social deficits and stereotypical behaviors in BTBR T+tf/J (BTBR) and valproic acid (VPA) experimental paradigms (56).

Improving hippocampal neurogenesis appears to be a novel strategy for ASD treatment (57). LXR β signaling regulates neurogenesis and enhances cognitive function (58–63). In 2019, Theofilopoulos et al. illustrated that 24(S),25-epoxycholesterol, the most potent and abundant LXR ligand in the developing mouse midbrain, along with cholesterol 24S-hydroxylase (CYP46A1) overexpression, facilitated midbrain dopaminergic neurogenesis in vivo (64). Notably, the 15q11.2 copy number variation (CNV) containing the CYFIP1 gene is associated with autism and schizophrenia. In 2024, De La Fuente et al. recently established a connection between LXR β deficiency and neurodevelopmental disorders (65). This study revealed that the strong interaction of LXR β with 24(S),25-epoxycholesterol is essential for neuronal maturation, while low activation of LXR β leads to maintenance of the neuronal precursor phenotype. The study delineates LXR-mediated oxysterol regulation of neurogenesis as a pathological mechanism in neural cells carrying the 15q11.2 CNV and provides a potential target for therapeutic strategies for associated disorders.

In 2024, Menteşe Babayigit et al. demonstrated that there is no association between the identified LXR β (rs2695121/rs17373080) single

nucleotide polymorphism and ASD (66). The study cohort comprised 107 children with autism (aged 2–18 years) and 103 age-matched children without autism. Despite the negative genetic association their data revealed that, compared to healthy developing children, those with ASD exhibited significantly higher levels of total cholesterol, low-density lipoprotein, and triglycerides, alongside markedly decreased levels of 27-hydroxycholesterol, suggesting its potential as a diagnostic marker for ASD.

Concluding Remarks

The available evidence suggests that LXR β plays a pivotal role in preventing CNS disease in experimental rodent paradigms. If these observations translate to humans, LXR β could emerge as a novel therapeutic target for treating neuropsychiatric disorders, particularly depression and anxiety. However, additional basic research and clinical trials are imperative to ascertain whether novel drugs targeting LXR β can be effectively utilized in the clinical treatment of neurological and neuropsychiatric diseases.

Declaration of Possible Conflicts of Interest

The contributors have confirmed that no conflict of interest exists.

Author Contributions

J.-Å. G. and XS conceived the review topic. XS wrote the draft and prepared tables. All authors revised the final manuscript and approved the final version.

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References

- Jakobsson T, Treuter E, Gustafsson JA, Steffensen KR. Liver X receptor biology and pharmacology: new pathways, challenges and opportunities. *Trends Pharmacol Sci.* 2012;33(7):394–404. DOI: [10.1016/j.tips.2012.03.013](https://doi.org/10.1016/j.tips.2012.03.013). PMID: 22541735
- Apfel R, Benbrook D, Lernhardt E, Ortiz MA, Salbert G, Pfahl M. A novel orphan receptor specific for a subset of thyroid hormone-responsive elements and its interaction with the retinoid/thyroid hormone receptor subfamily. *Mol Cell Biol.* 1994;14(10):7025–35. DOI: [10.1128/mcb.14.10.7025-7035.1994](https://doi.org/10.1128/mcb.14.10.7025-7035.1994). PMID: 7935418; PMCID: [PMC359232](https://pubmed.ncbi.nlm.nih.gov/PMC359232)
- Willy PJ, Umesono K, Ong ES, Evans RM, Heyman RA, Mangelsdorf DJ. LXR, a nuclear receptor that defines a distinct retinoid response pathway. *Genes Dev.* 1995;9(9):1033–45. DOI: [10.1101/gad.9.9.1033](https://doi.org/10.1101/gad.9.9.1033). PMID: 7744246



4. Teboul M, Enmark E, Li Q, Wikstrom AC, Pelto-Huikko M, Gustafsson JA. OR-1, a member of the nuclear receptor superfamily that interacts with the 9-cis-retinoic acid receptor. *Proc Nat Acad Sci USA*. 1995;92(6):2096–100. DOI: [10.1073/pnas.92.6.2096](https://doi.org/10.1073/pnas.92.6.2096). PMID: 7892230; PMCID: [PMC42430](https://pubmed.ncbi.nlm.nih.gov/PMC42430/)
5. Song C, Kokontis JM, Hiipakka RA, Liao S. Ubiquitous receptor: a receptor that modulates gene activation by retinoic acid and thyroid hormone receptors. *Proc Nat Acad Sci USA*. 1994;91(23):10809–13. DOI: [10.1073/pnas.91.23.10809](https://doi.org/10.1073/pnas.91.23.10809). PMID: 7971966; PMCID: [PMC45115](https://pubmed.ncbi.nlm.nih.gov/PMC45115/)
6. Shinar DM, Endo N, Rutledge SJ, Vogel R, Rodan GA, Schmidt A. NER, a new member of the gene family encoding the human steroid hormone nuclear receptor. *Gene*. 1994;147(2):273–6. DOI: [10.1016/0378-1119\(94\)90080-9](https://doi.org/10.1016/0378-1119(94)90080-9). PMID: 7926814
7. Seol W, Choi HS, Moore DD. Isolation of proteins that interact specifically with the retinoid X receptor: two novel orphan receptors. *Mol Endocrinol*. 1995;9(1):72–85. DOI: [10.1210/mend.9.1.7760852](https://doi.org/10.1210/mend.9.1.7760852). PMID: 7760852
8. Courtney R, Landreth GE. LXR Regulation of brain cholesterol: from development to disease. *Trends Endocrinol Metab*. 2016;27(6):404–14. DOI: [10.1016/j.tem.2016.03.018](https://doi.org/10.1016/j.tem.2016.03.018). PMID: 27113081; PMCID: [PMC4986614](https://pubmed.ncbi.nlm.nih.gov/PMC4986614/)
9. Zelcer N, Tontonoz P. Liver X receptors as integrators of metabolic and inflammatory signaling. *J Clin Invest*. 2006;116(3):607–14. DOI: [10.1172/JCI27883](https://doi.org/10.1172/JCI27883). PMID: 16511593; PMCID: [PMC1386115](https://pubmed.ncbi.nlm.nih.gov/PMC1386115/)
10. Gabbi C, Kong X, Suzuki H, Kim HJ, Gao M, Jia X, et al. Central diabetes insipidus associated with impaired renal aquaporin-1 expression in mice lacking liver X receptor beta. *Proc Nat Acad Sci USA*. 2012;109(8):3030–4. DOI: [10.1073/pnas.1200588109](https://doi.org/10.1073/pnas.1200588109). PMID: 22323586; PMCID: [PMC3286995](https://pubmed.ncbi.nlm.nih.gov/PMC3286995/)
11. Dai YB, Wu WF, Huang B, Miao YF, Nadarshina S, Warner M, et al. Liver X receptors regulate cerebrospinal fluid production. *Mol Psychiatry*. 2016;21(6):844–56. DOI: [10.1038/mp.2015.133](https://doi.org/10.1038/mp.2015.133). PMID: 26324101
12. Su W, Huang SZ, Gao M, Kong XM, Gustafsson JA, Xu SJ, et al. Liver X receptor beta increases aquaporin 2 protein level via a posttranscriptional mechanism in renal collecting ducts. *Am J Physiol Ren Physiol*. 2017;312(4):F619–28. DOI: [10.1152/ajprenal.00564.2016](https://doi.org/10.1152/ajprenal.00564.2016). PMID: 28052875
13. Laffitte BA, Chao LC, Li J, Walczak R, Hummasti S, Joseph SB, et al. Activation of liver X receptor improves glucose tolerance through coordinate regulation of glucose metabolism in liver and adipose tissue. *Proc Nat Acad Sci USA*. 2003;100(9):5419–24. DOI: [10.1073/pnas.0830671100](https://doi.org/10.1073/pnas.0830671100). PMID: 12697904; PMCID: [PMC154360](https://pubmed.ncbi.nlm.nih.gov/PMC154360/)
14. Miao Y, Wu W, Dai Y, Maneix L, Huang B, Warner M, et al. Liver X receptor beta controls thyroid hormone feedback in the brain and regulates browning of subcutaneous white adipose tissue. *Proc Nat Acad Sci USA*. 2015;112(45):14006–11. DOI: [10.1073/pnas.1519358112](https://doi.org/10.1073/pnas.1519358112). PMID: 26504234; PMCID: [PMC4653192](https://pubmed.ncbi.nlm.nih.gov/PMC4653192/)
15. Wang B, Tontonoz P. Liver X receptors in lipid signalling and membrane homeostasis. *Nat Rev Endocrinol*. 2018;14(8):452–63. DOI: [10.1038/s41574-018-0037-x](https://doi.org/10.1038/s41574-018-0037-x). PMID: 29904174; PMCID: [PMC6433546](https://pubmed.ncbi.nlm.nih.gov/PMC6433546/)
16. Schulman IG. Liver X receptors link lipid metabolism and inflammation. *FEBS Lett*. 2017;591(19):2978–91. DOI: [10.1002/1873-3468.12702](https://doi.org/10.1002/1873-3468.12702). PMID: 28555747; PMCID: [PMC5638683](https://pubmed.ncbi.nlm.nih.gov/PMC5638683/)
17. Korach-Andre M, Gustafsson JA. Liver X receptors as regulators of metabolism. *Biomol Concepts*. 2015;6(3):177–90. DOI: [10.1515/bmc-2015-0007](https://doi.org/10.1515/bmc-2015-0007). PMID: 25945723
18. Song X, Wu W, Warner M, Gustafsson JA. Liver X receptor regulation of glial cell functions in the CNS. *Biomedicines*. 2022;10(9):2165. DOI: [10.3390/biomedicines10092165](https://doi.org/10.3390/biomedicines10092165). PMID: 36140266; PMCID: [PMC9496004](https://pubmed.ncbi.nlm.nih.gov/PMC9496004/)
19. Song X, Wu W, Dai Y, Warner M, Nalvarte I, Antonson P, et al. Loss of ER-beta in aging LXRA/alpha knockout mice leads to colitis. *Int J Mol Sci*. 2023;24(15):12461. DOI: [10.3390/ijms241512461](https://doi.org/10.3390/ijms241512461). PMID: 37569842; PMCID: [PMC10419301](https://pubmed.ncbi.nlm.nih.gov/PMC10419301/)
20. Sweed N, Kim HJ, Hultenby K, Barros R, Parini P, Sancisi V, et al. Liver X receptor beta regulates bile volume and the expression of aquaporins and cystic fibrosis transmembrane conductance regulator in the gallbladder. *Am J Physiol Gastrointest Liver Physiol*. 2021;321(4):G243–51. DOI: [10.1152/ajpgi.00024.2021](https://doi.org/10.1152/ajpgi.00024.2021). PMID: 34259574; PMCID: [PMC8815792](https://pubmed.ncbi.nlm.nih.gov/PMC8815792/)
21. Hellemans KH, Hannaert JC, Denys B, Steffensen KR, Raemdonck C, Martens GA, et al. Susceptibility of pancreatic beta cells to fatty acids is regulated by LXR/PPARalpha-dependent stearyl-coenzyme A desaturase. *PLoS One*. 2009;4(9):e7266. DOI: [10.1371/journal.pone.0007266](https://doi.org/10.1371/journal.pone.0007266). PMID: 19787047; PMCID: [PMC2746288](https://pubmed.ncbi.nlm.nih.gov/PMC2746288/)
22. Song XY, Wu WF, Gabbi C, Dai YB, So M, Chaurasiya SP, et al. Retinal and optic nerve degeneration in liver X receptor beta knockout mice. *Proc Nat Acad Sci USA*. 2019;116(33):16507–12. DOI: [10.1073/pnas.1904719116](https://doi.org/10.1073/pnas.1904719116). PMID: 31371497; PMCID: [PMC6697819](https://pubmed.ncbi.nlm.nih.gov/PMC6697819/)
23. Song XY, Wu WF, Dai YB, Xu HW, Roman A, Wang L, et al. Ablation of Liver X receptor beta in mice leads to overactive macrophages and death of spinal ganglion neurons. *Hear Res*. 2022;422:108534. DOI: [10.1016/j.heares.2022.108534](https://doi.org/10.1016/j.heares.2022.108534). PMID: 35623301
24. Kainu T, Kononen J, Enmark E, Gustafsson JA, Pelto-Huikko M. Localization and ontogeny of the orphan receptor OR-1 in the rat brain. *J Mol Neurosci*. 1996;7(1):29–39. DOI: [10.1007/BF02736846](https://doi.org/10.1007/BF02736846). PMID: 8835780
25. Fan X, Kim HJ, Bouton D, Warner M, Gustafsson JA. Expression of liver X receptor beta is essential for formation of superficial cortical layers and migration of later-born neurons. *Proc Nat Acad Sci USA*. 2008;105(36):13445–50. DOI: [10.1073/pnas.0806974105](https://doi.org/10.1073/pnas.0806974105). PMID: 18768805
26. El-Hajjaji FZ, Oumeddour A, Pommier AJ, Ouvrier A, Viennois E, Dufour J, et al. Liver X receptors, lipids and their reproductive secrets in the male. *Biochim Biophys Acta*. 2011;1812(8):974–81. DOI: [10.1016/j.bbadis.2011.02.004](https://doi.org/10.1016/j.bbadis.2011.02.004). PMID: 21334438
27. Kim HJ, Andersson LC, Bouton D, Warner M, Gustafsson JA. Stromal growth and epithelial cell proliferation in ventral prostates of liver X receptor knockout mice. *Proc Nat Acad Sci USA*. 2009;106(2):558–63. DOI: [10.1073/pnas.0811295106](https://doi.org/10.1073/pnas.0811295106). PMID: 19122149; PMCID: [PMC2626742](https://pubmed.ncbi.nlm.nih.gov/PMC2626742/)
28. Steffensen KR, Robertson K, Gustafsson JA, Andersen CY. Reduced fertility and inability of oocytes to resume meiosis in mice deficient of the Lxr genes. *Mol Cell Endocrinol*. 2006;256(1–2):9–16. DOI: [10.1016/j.mce.2006.03.044](https://doi.org/10.1016/j.mce.2006.03.044). PMID: 16895745
29. Whitfield M, Ouvrier A, Cadet R, Damon-Soubeyrand C, Guiton R, Janny L, et al. Liver X receptors (LXRs) alpha and beta play distinct roles in the mouse epididymis. *Biol Reprod*. 2016;94(3):55. DOI: [10.1095/biolreprod.115.133538](https://doi.org/10.1095/biolreprod.115.133538). PMID: 26792941
30. Kim HJ, Fan X, Gabbi C, Yakimchuk K, Parini P, Warner M, et al. Liver X receptor beta (LXRbeta): a link between beta-sitosterol and amyotrophic lateral sclerosis-Parkinson's dementia. *Proc Nat Acad Sci USA*. 2008;105(6):2094–9. DOI: [10.1073/pnas.0711599105](https://doi.org/10.1073/pnas.0711599105). PMID: 18238900; PMCID: [PMC2542868](https://pubmed.ncbi.nlm.nih.gov/PMC2542868/)
31. Andersson S, Gustafsson N, Warner M, Gustafsson JA. Inactivation of liver X receptor beta leads to adult-onset motor neuron degeneration in male mice. *Proc Nat Acad Sci USA*. 2005;102(10):3857–62. DOI: [10.1073/pnas.0500634102](https://doi.org/10.1073/pnas.0500634102). PMID: 15738425; PMCID: [PMC553330](https://pubmed.ncbi.nlm.nih.gov/PMC553330/)
32. Bigini P, Steffensen KR, Ferrario A, Diomedea L, Ferrara G, Barbera S, et al. Neuropathologic and biochemical changes during disease progression in liver X receptor beta-/- mice, a model of adult neuron disease. *J Neuropathol Exp Neurol*. 2010;69(6):593–605. DOI: [10.1097/NEN.0b013e3181df20e1](https://doi.org/10.1097/NEN.0b013e3181df20e1). PMID: 20467332
33. Mouzat K, Chudinova A, Polge A, Kantar J, Camu W, Raoul C, et al. Regulation of brain cholesterol: what role do liver X receptors play in neurodegenerative diseases? *Int J Mol Sci*. 2019;20(16):3858. DOI: [10.3390/ijms20163858](https://doi.org/10.3390/ijms20163858). PMID: 31398791; PMCID: [PMC6720493](https://pubmed.ncbi.nlm.nih.gov/PMC6720493/)
34. Alnaaim SA, Al-Kuraishy HM, Alexiou A, Papadakis M, Saad HM, Batiha GE. Role of brain liver X receptor in parkinson's disease: hidden treasure and emerging opportunities. *Mol Neurobiol*. 2024;61(1):341–57. DOI: [10.1007/s12035-023-03561-y](https://doi.org/10.1007/s12035-023-03561-y). PMID: 37606719; PMCID: [PMC10791998](https://pubmed.ncbi.nlm.nih.gov/PMC10791998/)
35. Warner M, Gustafsson JA. Estrogen receptor beta and liver X receptor beta: biology and therapeutic potential in CNS diseases. *Mol Psychiatry*. 2015;20(1):18–22. DOI: [10.1038/mp.2014.23](https://doi.org/10.1038/mp.2014.23). PMID: 24662928
36. Mouzat K, Raoul C, Polge A, Kantar J, Camu W, Lumbroso S. Liver X receptors: from cholesterol regulation to neuroprotection—a new barrier against neurodegeneration in amyotrophic lateral sclerosis? *Cell Mol Life Sci*. 2016;73(20):3801–8. DOI: [10.1007/s00018-016-2330-y](https://doi.org/10.1007/s00018-016-2330-y). PMID: 27510420; PMCID: [PMC11108529](https://pubmed.ncbi.nlm.nih.gov/PMC11108529/)
37. Pineda-Torra I, Siddique S, Waddington KE, Farrell R, Jury EC. Disrupted lipid metabolism in multiple sclerosis: a role for liver X receptors? *Front Endocrinol (Lausanne)*. 2021;12:639757. DOI: [10.3389/fendo.2021.639757](https://doi.org/10.3389/fendo.2021.639757). PMID: 33927692; PMCID: [PMC8076792](https://pubmed.ncbi.nlm.nih.gov/PMC8076792/)
38. Peng Z, Deng B, Jia J, Hou W, Hu S, Deng J, et al. Liver X receptor beta in the hippocampus: A potential novel target for the treatment of major depressive disorder? *Neuropharmacology*. 2018;135:514–28. DOI: [10.1016/j.neuropharm.2018.04.014](https://doi.org/10.1016/j.neuropharm.2018.04.014). PMID: 29654801
39. Han S, Yuan X, Zhao F, Manyande A, Gao F, Wang J, et al. Activation of LXRs alleviates neuropathic pain-induced cognitive dysfunction by modulation of microglia polarization and synaptic plasticity via PI3K/AKT pathway. *Inflamm Res*. 2024;73(2):157–74. DOI: [10.1007/s00011-023-01826-9](https://doi.org/10.1007/s00011-023-01826-9). PMID: 38183431
40. Bogie JFJ, Vanmierlo T, Vanmol J, Timmermans S, Mailleux J, Nelissen K, et al. Liver X receptor beta deficiency attenuates autoimmune-associated neuroinflammation in a T cell-dependent manner. *J Autoimmun*. 2021;124:102723. DOI: [10.1016/j.jaut.2021.102723](https://doi.org/10.1016/j.jaut.2021.102723). PMID: 34481107
41. Qiu C, Wang M, Yu W, Rong Z, Zheng HS, Sun T, et al. Activation of the hippocampal LXRbeta improves sleep-deprived cognitive impairment by inhibiting neuroinflammation. *Mol Neurobiol*. 2021;58(10):5272–88. DOI: [10.1007/s12035-021-02446-2](https://doi.org/10.1007/s12035-021-02446-2). PMID: 34278533
42. Endo-Umeda K, Kim E, Thomas DG, Liu W, Dou H, Yalcinkaya M, et al. Myeloid LXR (liver X receptor) deficiency induces inflammatory gene expression in foamy macrophages and accelerates atherosclerosis. *Arterioscler Thromb Vasc Biol*.



- 2022;42(6):719–31. DOI: [10.1161/ATVBAHA.122.317583](https://doi.org/10.1161/ATVBAHA.122.317583). PMID: 35477277; PMCID: [PMC9162499](https://pubmed.ncbi.nlm.nih.gov/PMC9162499/)
43. Zhang R, Dong Y, Liu Y, Moezzi D, Ghorbani S, Mirzaei R, et al. Enhanced liver X receptor signalling reduces brain injury and promotes tissue regeneration following experimental intracerebral haemorrhage: roles of microglia/macrophages. *Stroke Vasc Neurol*. 2023;8(6):486–502. DOI: [10.1136/svn-2023-002331](https://doi.org/10.1136/svn-2023-002331). PMID: 37137522; PMCID: [PMC10800269](https://pubmed.ncbi.nlm.nih.gov/PMC10800269/)
 44. Xu X, Xiao X, Yan Y, Zhang T. Activation of liver X receptors prevents emotional and cognitive dysfunction by suppressing microglial M1-polarization and restoring synaptic plasticity in the hippocampus of mice. *Brain Behav Immun*. 2021;94:111–24. DOI: [10.1016/j.bbi.2021.02.026](https://doi.org/10.1016/j.bbi.2021.02.026). PMID: 33662504
 45. Li J, Zhu P, Li Y, Xiao K, Tang J, Liang X, et al. The liver X receptors agonist GW3965 attenuates depressive-like behaviors and suppresses microglial activation and neuroinflammation in hippocampal subregions in a mouse depression model. *J Comp Neurol*. 2022;530(16):2852–67. DOI: [10.1002/cne.25380](https://doi.org/10.1002/cne.25380). PMID: 35758275
 46. Li C, Wu H, Na HST, Wang L, Zhong C, Deng B, et al. Neuronal-microglial liver X receptor beta activating decrease neuroinflammation and chronic stress-induced depression-related behavior in mice. *Brain Res*. 2022;1797:148112. DOI: [10.1016/j.brainres.2022.148112](https://doi.org/10.1016/j.brainres.2022.148112). PMID: 36216100
 47. Li Y, He X, Zhang J, Zhou Q, Liu X, Zhou G. Medecarbin improves depressive-like behaviors in a chronic unpredictable mild stress-induced mouse model of depression by upregulating liver X receptor beta expression in the amygdala. *Neurotox Res*. 2022;40(6):1937–47. DOI: [10.1007/s12640-022-00610-7](https://doi.org/10.1007/s12640-022-00610-7). PMID: 36445678
 48. Zhu P, Tang J, Liang X, Luo Y, Wang J, Li Y, et al. Activation of liver X receptors protects oligodendrocytes in CA3 of stress-induced mice. *Front Pharmacol*. 2022;13:936045. DOI: [10.3389/fphar.2022.936045](https://doi.org/10.3389/fphar.2022.936045). PMID: 35959443; PMCID: [PMC9358133](https://pubmed.ncbi.nlm.nih.gov/PMC9358133/)
 49. Maas DA, Martens MB, Priovoulos N, Zuure WA, Homberg JR, Nait-Oumesmar B, et al. Key role for lipids in cognitive symptoms of schizophrenia. *Transl Psychiatry*. 2020;10(1):399. DOI: [10.1038/s41398-020-01084-x](https://doi.org/10.1038/s41398-020-01084-x). PMID: 33184259; PMCID: [PMC7665187](https://pubmed.ncbi.nlm.nih.gov/PMC7665187/)
 50. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. *Dialogues Clin Neurosci*. 2015;17(3):327–35. DOI: [10.31887/DCNS.2015.17.3/bbandelow](https://doi.org/10.31887/DCNS.2015.17.3/bbandelow). PMID: 26487813; PMCID: [PMC4610617](https://pubmed.ncbi.nlm.nih.gov/PMC4610617/)
 51. Tan XJ, Dai YB, Wu WF, Warner M, Gustafsson JA. Anxiety in liver X receptor beta knockout female mice with loss of glutamic acid decarboxylase in ventromedial prefrontal cortex. *Proc Natl Acad Sci USA*. 2012;109(19):7493–8. DOI: [10.1073/pnas.1205189109](https://doi.org/10.1073/pnas.1205189109). PMID: 22529354; PMCID: [PMC3358830](https://pubmed.ncbi.nlm.nih.gov/PMC3358830/)
 52. Xu P, Xu H, Tang X, Xu L, Wang Y, Guo L, et al. Liver X receptor beta is essential for the differentiation of radial glial cells to oligodendrocytes in the dorsal cortex. *Mol Psychiatry*. 2014;19(8):947–57. DOI: [10.1038/mp.2014.60](https://doi.org/10.1038/mp.2014.60). PMID: 24934178
 53. Li X, Zhong H, Wang Z, Xiao R, Antonson P, Liu T, et al. Loss of liver X receptor beta in astrocytes leads to anxiety-like behaviors via regulating synaptic transmission in the medial prefrontal cortex in mice. *Mol Psychiatry*. 2021;26(11):6380–93. DOI: [10.1038/s41380-021-01139-5](https://doi.org/10.1038/s41380-021-01139-5). PMID: 33963286
 54. Yu W, Wang L, Yang L, Li YJ, Wang M, Qiu C, et al. Activation of LXRbeta signaling in the amygdala confers anxiolytic effects through rebalancing excitatory and inhibitory neurotransmission upon acute stress. *Neurotherapeutics*. 2020;17(3):1253–70. DOI: [10.1007/s13311-020-00857-y](https://doi.org/10.1007/s13311-020-00857-y). PMID: 32297184; PMCID: [PMC7609627](https://pubmed.ncbi.nlm.nih.gov/PMC7609627/)
 55. Cai Y, Tang X, Chen X, Li X, Wang Y, Bao X, et al. Liver X receptor beta regulates the development of the dentate gyrus and autistic-like behavior in the mouse. *Proc Natl Acad Sci USA*. 2018;115(12):E2725–33. DOI: [10.1073/pnas.1800184115](https://doi.org/10.1073/pnas.1800184115). PMID: 29507213; PMCID: [PMC5866608](https://pubmed.ncbi.nlm.nih.gov/PMC5866608/)
 56. Cai Y, Zhong H, Li X, Xiao R, Wang L, Fan X. The liver X receptor agonist T0901317 ameliorates behavioral deficits in two mouse models of autism. *Front Cell Neurosci*. 2019;13:213. DOI: [10.3389/fncel.2019.00213](https://doi.org/10.3389/fncel.2019.00213). PMID: 31139052; PMCID: [PMC6527842](https://pubmed.ncbi.nlm.nih.gov/PMC6527842/)
 57. Liu C, Liu J, Gong H, Liu T, Li X, Fan X. Implication of hippocampal neurogenesis in autism spectrum disorder: pathogenesis and therapeutic implications. *Curr Neuropharmacol*. 2023;21(11):2266–82. DOI: [10.2174/1570159X21666221220155455](https://doi.org/10.2174/1570159X21666221220155455). PMID: 36545727; PMCID: [PMC10556385](https://pubmed.ncbi.nlm.nih.gov/PMC10556385/)
 58. Chen L, Song D, Chen B, Yang X, Cheng O. Activation of liver X receptor promotes hippocampal neurogenesis and improves long-term cognitive function recovery in acute cerebral ischemia-reperfusion mice. *J Neurochem*. 2020;154(2):205–17. DOI: [10.1111/jnc.14890](https://doi.org/10.1111/jnc.14890). PMID: 31602646
 59. Sun T, Li YJ, Tian QQ, Wu Q, Feng D, Xue Z, et al. Activation of liver X receptor beta-enhancing neurogenesis ameliorates cognitive impairment induced by chronic cerebral hypoperfusion. *Exp Neurol*. 2018;304:21–9. DOI: [10.1016/j.expneurol.2018.02.006](https://doi.org/10.1016/j.expneurol.2018.02.006). PMID: 29447944
 60. Sacchetti P, Sousa KM, Hall AC, Liste I, Steffensen KR, Theofilopoulos S, et al. Liver X receptors and oxysterols promote ventral midbrain neurogenesis in vivo and in human embryonic stem cells. *Cell Stem Cell*. 2009;5(4):409–19. DOI: [10.1016/j.stem.2009.08.019](https://doi.org/10.1016/j.stem.2009.08.019). PMID: 19796621
 61. Theofilopoulos S, Wang Y, Kitambi SS, Sacchetti P, Sousa KM, Bodin K, et al. Brain endogenous liver X receptor ligands selectively promote midbrain neurogenesis. *Nat Chem Biol*. 2013;9(2):126–33. DOI: [10.1038/nchembio.1156](https://doi.org/10.1038/nchembio.1156). PMID: 23292650
 62. Theofilopoulos S, Arenas E. Liver X receptors and cholesterol metabolism: role in ventral midbrain development and neurodegeneration. *F1000Prime Rep*. 2015;7:37. DOI: [10.12703/P7-37](https://doi.org/10.12703/P7-37). PMID: 26097711; PMCID: [PMC4447034](https://pubmed.ncbi.nlm.nih.gov/PMC4447034/)
 63. Sandoval-Hernandez AG, Hernandez HG, Restrepo A, Munoz JI, Bayon GF, Fernandez AF, et al. Liver X receptor agonist modifies the DNA methylation profile of synapse and neurogenesis-related genes in the triple transgenic mouse model of alzheimer's disease. *J Mol Neurosci*. 2016;58(2):243–53. DOI: [10.1007/s12031-015-0665-8](https://doi.org/10.1007/s12031-015-0665-8). PMID: 26553261
 64. Theofilopoulos S, Abreu de Oliveira WA, Yang S, Yutuc E, Saeed A, Abdel-Khalik J, et al. 24(S),25-Epoxycholesterol and cholesterol 24S-hydroxylase (CYP46A1) overexpression promote midbrain dopaminergic neurogenesis in vivo. *J Biol Chem*. 2019;294(11):4169–76. DOI: [10.1074/jbc.RA118.005639](https://doi.org/10.1074/jbc.RA118.005639). PMID: 30655290 PMCID: [PMC6422085](https://pubmed.ncbi.nlm.nih.gov/PMC6422085/)
 65. De La Fuente DC, Tamburini C, Stonelake E, Andrews R, Hall J, Owen MJ, et al. Impaired oxysterol-liver X receptor signaling underlies aberrant cortical neurogenesis in a stem cell model of neurodevelopmental disorder. *Cell Rep*. 2024;43(3):113946. DOI: [10.1016/j.celrep.2024.113946](https://doi.org/10.1016/j.celrep.2024.113946). PMID: 38483902
 66. Menteşe Babayigit T, Gümüş-Akay G, Uytun MÇ, Doğan Ö, Serdar MA, Efendi GY, et al. Investigation of liver X receptor gene variants and oxysterol dysregulation in autism spectrum disorder. *Children*. 2024;11(5):551. DOI: [10.3390/children11050551](https://doi.org/10.3390/children11050551). PMID: 38790546; PMCID: [PMC1120122](https://pubmed.ncbi.nlm.nih.gov/PMC1120122/)

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