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Therapeutic potential of liver X receptor beta in depression and anxiety

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Liver X receptors (LXRs), particularly LXRβ, 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 LXRβ'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, LXRβ 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 LXRβ research into clinical interventions, emphasizing the potential for personalized medicine approaches in psychiatry. This bench-to-bedside article underscores the importance of LXRβ 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: LXRβ

Liver X receptors, LXRα and LXRβ, 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 LXRα. Our laboratory discovered LXRβ, 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 LXRα led to its current name, LXRβ.

LXRα 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, LXRβ'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 LXRβ's wide-ranging effects throughout the body.

Research on LXRα 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, LXRβ shows a broader tissue distribution. While its liver expression is minimal, LXRβ 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 LXRα and LXRβ are present in reproductive tissues like the ovary, testis, prostate epithelium, and epididymis, 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 LXRβ 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 LXRβ in Depression

Studies have demonstrated LXRβ'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 LXRβ 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 LXRβ in Anxiety

Anxiety disorders are the most prevalent psychiatric conditions (50). Female mice lacking LXRβ 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 LXRβ effects on depression-like and anxiety-like behaviors in experimental rodent paradigms

Neuropsychiatric-related behaviors	Experimental paradigm	LXRβ 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-κB signaling and NLRP3 inflammasome activation	(46)
Anxiety-like	LXRβ-deficient female mice	–	Decreased glutamic acid decarboxylase (65+67) in the ventromedial PFC	(51)
	LXRβ-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 LXRβ-deficient mice	–	Impaired synaptic transmission in mPFC	(53)

synthesis, in the ventromedial prefrontal cortex (PFC). Further studies demonstrated that loss of LXRβ 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 LXRβ from astrocytes resulted in anxiety-like, but not depression-like behaviors in adult male mice (53). This work suggests that astrocytic LXRβ 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 LXRβ signaling activation in the amygdala (54).

Role of LXRβ 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. LXRβ-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). LXRβ 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 LXRβ deficiency and neurodevelopmental disorders (65). This study revealed that the strong interaction of LXRβ with 24(S),25-epoxycholesterol is essential for neuronal maturation, while low activation of LXRβ 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 Babayiğit et al. demonstrated that there is no association between the identified LXRβ (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 LXRβ plays a pivotal role in preventing CNS disease in experimental rodent paradigms. If these observations translate to humans, LXRβ 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 LXRβ 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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