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THOUGHT LEADERS INVITED REVIEW

Liver X and thyroid hormone receptors in neurodegeneration

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The role of thyroid hormone (TH) in the development and function of the central nervous system (CNS) has been known for many years. However, the role of liver X receptors (LXRs) in TH function and protection against neuronal degeneration was not recognized until recently. The relationship between thyroid hormone receptors (TRs) and LXRs became apparent with the cloning of steroid hormone receptors, leading to the discovery of the nuclear receptor superfamily. This family includes not only receptors for classical steroid hormones but also many newly discovered ligand-activated nuclear receptors. LXRs and TRs regulate overlapping pathways in lipid and carbohydrate metabolism, as well as in overall CNS development and function. These CNS pathways include neuronal migration during cortical and cerebellar layering, myelination, oligodendrocyte maturation, microglial activation, and astrocyte functions. Furthermore, LXRs likely have unique functions, as evidenced by the inability of TH to compensate for microglial activation, oligodendrocyte maturation, spinal motor neuron death, and degeneration of retinal and cochlear neurons in LXRβ knockout mice. The common and unique functions of these two receptors are the subject of this review. We analyzed some of the most relevant literature on the regulation and function of LXRs and TRs and investigated why both receptors are required in the human body. We conclude that LXRs and TRs do not represent parallel pathways but rather constitute a single pathway through which the TH endocrine system regulates cholesterol homeostasis. Subsequently, LXRs, activated by cholesterol metabolites, function as a paracrine/autocrine system that modulates the target cell response to TH.

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Historical Perspective: LXRs

Liver X receptors (LXRs, LXRα, and LXRβ) belong to a subfamily of the nuclear receptor superfamily of ligand-activated transcription factors, which comprises 48 members in the human genome (1). Nuclear receptors play crucial roles in regulating metabolism, endocrine systems, and the development and function of the central nervous system (CNS). Although the functions of thyroid hormone (TH) have been studied for many years, LXRs were only discovered in the 1990s. Thyroid hormone receptors (TRs), TRα and TRβ, are differentially expressed in various tissues and have distinct roles in TH signaling (2). LXRβ (gene name *NR1H2*) was independently discovered by several laboratories (3–6) in 1996 and was initially designated as OR1, UR, NER, and RIP-15. It was later renamed LXRβ due to its homology with LXRα (also known as *NR1H3*), a receptor discovered in 1994 (7, 8).

LXRα has two major functions in the body: lipid metabolism in organs such as the liver, intestine, and adipose tissue, and regulation of the immune system, notably in macrophages (9). LXRβ has a broader tissue distribution than LXRα; while its expression in the liver is low, LXRβ is well expressed in immune system cells, glial cells in the CNS, colon, gallbladder, pancreatic islets, retina, and inner ear (10–16). Although it is expressed in very few neurons in the adult mouse brain (17), LXRβ is widely expressed in neurons of the fetal brain (18, 19). Both LXRα and LXRβ are expressed in the ovary, testis, prostate epithelium, and epididymis, where they play significant roles (20–23).

While the most well-studied function of LXRs is their role in cholesterol homeostasis (24), a function shared with TRs, cholesterol transport is just one of many transport functions of LXRs. Like TRs, LXRs regulate the transport of water by modulating aquaporins (25–29) and glucose through GLUT4 regulation (30–32). In addition, LXRs regulate the transport of THs and lactate through monocarboxylate transporters MCT8 and MCT10 (33). Transport of lactate into neurons is essential for neuronal nutrition, and its regulation by LXRβ (via MCT1) may explain the loss of neurons in LXR$\beta^{-/-}$ mice.

Classical hormones such as androgens, estrogens, progesterone, glucocorticoids, and thyroid hormone function in endocrine pathways where glands (such as the testis, ovaries, adrenal glands, and thyroid gland) secrete hormones into the bloodstream, which target organs receive via the vascular system. With the exception of the vitamin D receptor, more recently discovered members of the nuclear receptor superfamily are activated by ligands not secreted from endocrine glands but rather synthesized in various cells throughout the body. In some cases, ligands are acquired from the diet or are pharmaceutical agents. The natural ligands of LXRs are oxygenated metabolites of cholesterol (oxysterols). Some cells that synthesize oxysterols also express LXRs, making the LXR system an autocrine and paracrine system rather than a purely endocrine one.

The two major differences between TH and LXR signaling are: 1) TH governs the regulation and integration of metabolic homeostasis at the hypothalamic-pituitary level, but LXR does not; and 2) since oxysterols are not circulating hormones, LXR activation is not necessarily determined by plasma levels of oxysterols (34).

It is important to note that even classical steroid receptors can act in a paracrine manner. For example, dihydrotestosterone (DHT), a ligand for the androgen receptor, is not a circulating hormone but is synthesized from testosterone in cells expressing the enzyme steroid 5α-reductases. Similarly, 3β-Adiol (5α-androstane-3β,17β-diol), a ligand for estrogen receptor beta (35), is synthesized in cells expressing steroid 5α-reductase and 17β-hydroxysteroid dehydrogenase type 6 (36). If TH and LXR have a relationship similar to that of testosterone and DHT, the effects of TH in cells may vary depending on LXR expression.

Although LXR signaling is not regulated by the hypothalamic–pituitary–thyroid axis, LXR does regulate thyrotropin-releasing hormone (TRH). By mediating TH's action on TRH release, LXR influences

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thyroid-stimulating hormone (TSH) levels. In the absence of LXR, there is excessive TSH release, which stimulates thyroxine (T4) release from the thyroid gland. In addition, because LXR represses deiodinases, the loss of LXR can create a hyperthyroid state, which may help explain why LXR$\beta^{-/-}$ mice are resistant to obesity induced by a high-fat diet (33).

LXRs and TRs

The function of THs is mainly mediated through their binding to TRs at specific TREs (thyroid response elements) on DNA. Both TRs and LXRs bind to these response elements, which consist of direct repeats of the half-site sequence 5′-G/AGGTCA-3′, separated by four nucleotides (DR4). In the absence of their ligands, both TRs and LXRs bind to DR4, recruiting corepressors and inhibiting the transcription of responsive genes. When ligands bind, they relieve this repression by causing the release of corepressors and subsequent binding of coactivators, leading to the activation of transcription of responsive genes (37).

TRs can bind to DNA either as homodimers or as heterodimers with retinoid X receptors (RXRs), while LXRs form obligatory heterodimers with RXR (38–40). RXRs are a subgroup of the nuclear receptor superfamily, comprising isotypes α, β, and γ, which can form homodimeric and heterodimeric complexes with other nuclear receptors (41). The endogenous ligand for RXR is 9-cis retinoic acid (42). Thus, vitamin A also plays a significant role in the regulation of the immune system by TH and LXR (43).

T3, T4, and Deiodinases

T4 is a prohormone that is converted to the active hormone triiodothyronine (T3) through the action of deiodinases. The local activation of T4 to active T3 by deiodinases is a key mechanism of TH regulation of metabolism. There are two activating deiodinases, DIO1 and DIO2, and one inactivating deiodinase, DIO3 (44, 45). In humans, DIO1 is highly expressed in the liver, while DIO2 is expressed in the hypothalamus, white fat, skeletal muscle, and brown adipose tissue, where it is essential for adaptive thermogenesis (46). One key mechanism by which LXR regulates TH function in both rodents (47) and humans (48) is through the downregulation of deiodinases.

Some Complexities of LXRs and TRs Signaling in the Brain

Since cholesterol cannot cross the blood–brain barrier (BBB), it must be synthesized within the brain. Astrocytes are responsible for cholesterol synthesis, which is then transported to other cells via the transport protein apolipoprotein E (ApoE) (49, 50). Additionanally, the brain synthesizes two oxysterols: 25-hydroxycholesterol (25-HC), produced in microglia (51), and 24-hydroxycholesterol (24-HC), which is catalyzed by the enzyme CYP46A1 (cholesterol 24-hydroxylase) and expressed in neurons of the hippocampus, cortex, Purkinje cells of the cerebellum, and interneurons in the hippocampus and cerebellum (52). 24-HC is a major metabolite of cholesterol in the brain and serves as the route for excreting excess cholesterol (53, 54). Furthermore, the brain can inactivate oxysterols through CYP7B1, which catalyzes hydroxylation of oxysterols at the 6 and 7 positions (55). Although the cellular distribution of CYP7B1 has not been well investigated, it is one of the most active cytochrome P450 enzymes in the brain (56), making it very unlikely that the cells harboring this enzyme will respond to oxysterols.

T3 does not cross the BBB, but T4 does. Therefore, deiodinases are extremely important for the TH function in the brain, and defective deiodinases can lead to brain TH deficiency. TH enters the brain either directly via the BBB or indirectly via the blood–cerebrospinal fluid (CSF) barrier, with the BBB serving as the primary entry path for T4 (57). TH enters the choroid plexus through transmembrane transporters MCT8 and organic anion-transporting polypeptide 1C1 (OATP1C1) and exits the choroid plexus to enter the CSF via TH transmembrane transporters or through choroid plexus-derived transthyretin secreted into the CSF (58). DIO2 is expressed in the choroid plexus (59). LXRs regulate CSF dynamics at both the choroid plexus and the astrocytic end feet, and inactivation of LXR results in degeneration of the choroid plexus and lack of CSF in the lateral ventricles (28). This degeneration, along with the loss of DIO2, leads to reduced TH levels in the brain. Consequently, some phenotypic aspects of LXR knockout mice resemble TH deficiency. Once THs have passed BBB, their local availability depends on the activity of the astrocytic DIO2 to convert T4 to T3. T3 is subsequently inactivated in neurons by DIO3, which removes the 3′ iodine, producing 3,5-diiodothyronine (T2).

In addition to regulating deiodinases, LXRs also regulate T4 transporters. In humans, as in other primates, the BBB contains MCT8 but lacks OATP1C1 (60, 61). MCT8 is a highly specific transmembrane TH transporter responsible for the cellular influx and efflux of T4 and T3 (62). It is indespensible for driving TH-dependent oligodendrocyte differentiation and, consequently, myelination (63, 64). In humans, mutations in *SLC16A2*, the gene encoding MCT8, lead to an X-linked syndrome characterized by severe neurological impairment and altered T3 concetrations due to impaired TH uptake in the developing brain. In mice lacking both MCT8 and OATP1C1, TH concentrations in the brain are significantly affected (65).

Both TRs and LXRs bind to DR4 on DNA in the absence of their respective ligands, repreesing genes regulated by DR4 response elements. The knockout of LXR relieves repression on DR4-responsive genes; however, what cannot occur in LXR knockout mice is the activation of LXR by ligands and the recruitment of coactivators to enhance the transcription of LXR-responsive genes. To understanding the phenotype of LXR knocknout mice, we must consider both the derepression of certain genes and the absence of activation of others by LXR ligands.

TH regulates metabolic rate, body temperature, cholesterol homeostasis, and adrenergic function. Of these, only adrenergic stimulation is not shared by LXRs. TH regulates cholesterol homeostasis at two major points: it increases the low-density lipoprotein (LDL) receptor to facilitate cholesterol removal from circulation and stimulates cholesterol 7alpha-hydroxylase (CYP7A) to promote cholesterol removal from the body in the form of bile acids. LXRs act as cholesterol sensors, activated by cholesterol metabolites (1). Upon activation, they assist TH in eliminating cholesterol from the body by inducing cholesterol transporters ABCA1 and ABCG1, which transport cholesterol out of cells. However, LXRs also act at multiple levels to reduce TH function: 1) LXR reduces deiodinases, preventing the conversion of T4 to T3; 2) LXR lowers TH levels by facilitating negative feedback at the hypothalamic level; and 3) LXR induces the expression of the inducible degrader of the LDL receptor (IDOL), which decreases LDL receptor expression on the cell surface and limits LDL/cholesterol uptake (66).

LXRs and TRs in Neurodegeneration

Both LXR and TH are essential for normal brain development, influencing neurogenesis, neuronal and glial cell differentiation and migration, synaptogenesis, and myelination during early fetal life (67, 68). Dysregulation of cholesterol metabolism in the CNS has been linked to several neurological disorders (49, 69–74). Preclinical studies have indicated that LXRs and TRs can be used as targets for the treatment of neurodegenerative diseases (Figure 1), such as Alzheimer's disease (AD) , Parkinson's disease (75, 76), amyotrophic lateral sclerosis (ALS) (77), Huntington's disease, and multiple sclerosis (MS) (78).

Although these common and devastating neurodegenerative diseases are associated with aging, neurodegeneration likely begins much earlier, as disease symptoms emerge only after a significant number of neurons have already been lost. Our studies have shown marked expression of LXRβ in cortical neurons in the fetal mouse brain during later embryonic stages (19). LXRβ expression first appears in the cerebral cortex as early as E14.5 and is strongly expressed in the cortex plate from E16.5 until E18.5. After birth, LXRβ is mainly localized in cortical layers II/III. In LXR$\beta^{-/-}$ mice, there is no defect in neuronal proliferation; however, later-born neurons fail to migrate to cortical layers II/III as they do in wild-type (WT) littermates (19). This migration defect is thought to result from a defect in radial glia and reduced expression of the renin receptor, ApoER2 (79). The defect is corrected when TH levels increase, and by postnatal day 14, there is no detectable difference in the cortex between WT and LXR$\beta^{-/-}$ mice (79). These observations suggest that in the absence of LXRβ, there is insufficient TH in the fetal brain, leading to a prolonged repressive role of TR- on TH-responsive genes.

Despite the well-known effects of TH in the developing brain and the clear role of fetal hypothyroidism in mental retardation, TH is not implicated in late-onset neurodegenerative diseases. However, the loss of

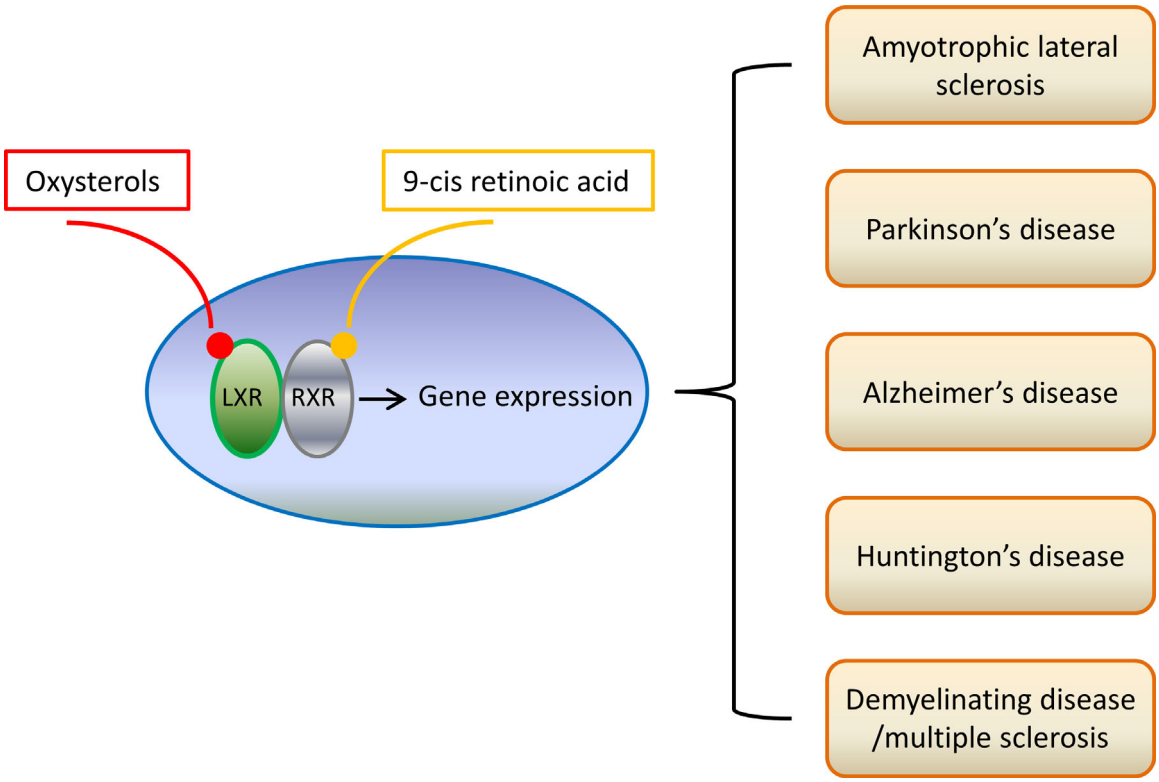

Figure 1. LXR and related CNS neurological disorders.

LXRβ in mice does lead to age-related neurodegeneration. In LXR$\beta^{-/-}$ mice, there is a loss of dopaminergic (DA) neurons in the substantia nigra (80), large motor neurons in the ventral horn of the spinal cord (81), epithelial cells of the choroid plexus (28), retinal ganglion cells (15), and spiral ganglion neurons (Figure 2) (16). All of these conditions develop with age after the mice are 6 months of age.

One perplexing observation, in view of the loss of DA and motor neurons, is the absence of LXRβ expression in these neurons in adult mice. This has led to the conclusion that LXRβ in cells other than DA and motor neurons protects these neurons from age-related loss. These specific cell types involved remain to be identified. To date, LXRβ has been specifically deleted from astrocytes (82) and microglia, and there was no observed loss of DA or motor neurons in these mice. It remains possible that degeneration of the choroid plexus and defects in CSF, which occur in the absence of LXR, are major contributors to the neurodegeneration observed in LXR$\beta^{-/-}$ mice.

LXRs and TRs in ALS

ALS is a late-onset, fatal neurodegenerative disorder characterized by the specific loss of both upper and lower motor neurons (83). The majority of cases are classified as sporadic, with the etiology remaining unknown. Less than 10% of ALS cases are familial and associated with defects in the *SOD1*, *C9ORF72*, *FUS*, and *TARDBP* genes. Although none of these genes are regulated by LXR, a proteomic analysis of serum from ALS patients revealed that the LXR/RXR pathway is one of the most significantly regulated pathways, with both LXRα and LXRβ identified as genetic modulators of the ALS phenotype (84, 85). In mice lacking LXRβ, there is progressive impairment of motor performance leading to hind limb paralysis, loss of motor neurons in the ventral horn of the spinal cord (Figure 3), and loss of neuromuscular junctions (80, 81, 86).

A study on the pathogenesis of ALS indicated that 25-HC, an endogenous ligand for LXR, may actively mediate neuronal apoptosis, particularly in the early symptomatic stage of the disease (87). The failure of the CNS to remove excess cholesterol can lead to neurodegeneration, as the accumulation of cholesterol may be toxic to neuronal cells. However, cholesterol accumulation is not the only brain defect caused by defective LXR; there is also a reduction in 3β,7α-dihydroxycholest-5-en-26-oic acid, a neuroprotective cholesterol metabolite (88, 89).

Another common defect observed in both ALS and LXR$\beta^{-/-}$ mice is the structural and functional disruption of the blood–CSF barrier. In ALS, there is disruption of junctions between choroid plexus epithelial cells, activation of platelets, immune infiltration into the choroid plexus, and degeneration of major vasculature associated with the disease (90). The choroid plexus of LXR knockout mice is severely affected (28), with degeneration and absence of CSF in the lateral ventricles being prominent characteristics of the LXR$^{-/-}$ mouse brain.

To date, studies have not provided strong evidence to support a role for TH in ALS. In a cohort of Portuguese patients with ALS, thyroid dysfunction was not associated with the disease (91), and in a cohort from Southwest China, thyroid dysfunction did not associated with survival or serve as a prognostic factor for ALS (92). Despite the lack of effect of TH on ALS, a similar movement disorder is observed in both TH and LXR deficiencies: pronounced, spontaneous, asymmetrical circling behavior. This behavior was first reported by Kincaid (93) in genetically hypothyroid mice, which does not develop a thyroid gland due to a defective TSH gene. The circling behavior appeared in both male and female mice around postnatal day 35 and persisted throughout their lifespan. The circling was unidirectional, either clockwise or counterclockwise. This behavior was noted in all female but not male LXR$\beta^{-/-}$ mice. In the Kincaid study, the cycling was linked to the loss of DA neurons in the substantia nigra, but it remains unclear why the behavior only emerged in adult mice. In the LXR$\beta^{-/-}$ mice, a similar cycling behavior was observed, though its etiology has not been thoroughly investigated.

LXRs and TRs in Dopaminergic Neurons

In the developing mouse brain at E11.5, the LXR agonist 24(S),25-epoxycholesterol increased midbrain DA neurogenesis from precursor cells by about 40% *in vitro* and *in vivo* (94–96). The LXR-regulated transcription factor responsible for this increase in the differentiation of radial glia into DA neurons was identified as the basic helix-loop-helix

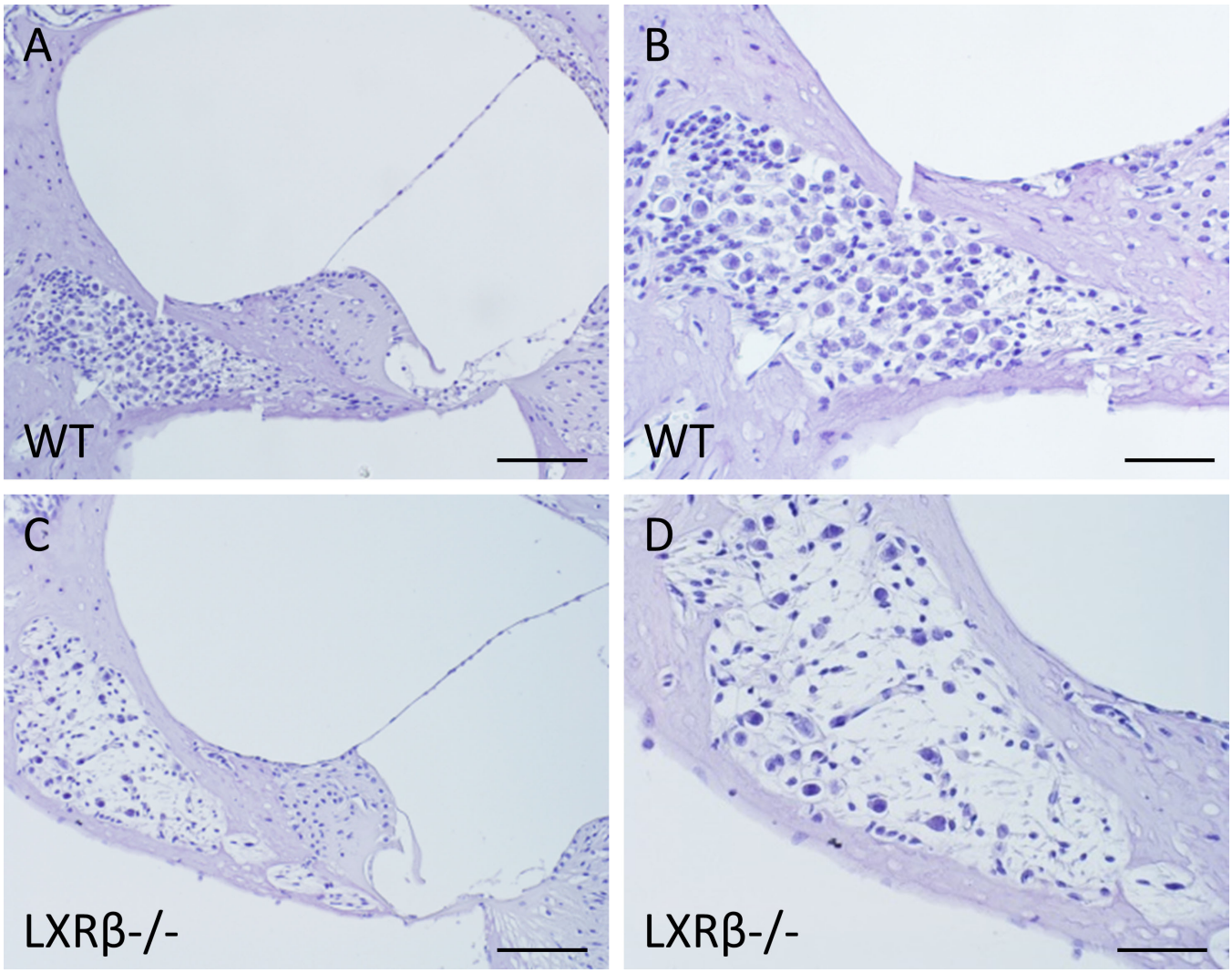

Figure 2. The number of spiral ganglion neurons in the cochlea of LXR$\beta^{-/-}$ mice is less than that of WT mice. 12 months of age. Scale bars: A and C, 100 μm; B and D, 50 μm.

transcription factor SREBP1 (sterol regulatory element binding protein 1; gene name *Srebf1*) (97). Despite this role of LXRβ in the differentiation of DA neurons, there is no apparent reduction in the number of DA neurons in the substantia nigra in 5-month-old LXR$\beta^{-/-}$ mice, and their performance on the rotarod test was comparable to that of WT mice (80). Thus, there is a disconnect between LXR's actions in the fetal development of DA neurons *in vitro* and its role in the adult brain.

Knocking out LXR affects the survival of DA neurons. In the substantia nigra of LXR$\beta^{-/-}$ mice, the loss of DA neurons begins to be noticeable after the mice reach 6 months of age, and by 16 months, there is a marked reduction in the number of DA neurons. These mice perform poorly on the rotarod. LXRβ knockout mice also show increased sensitivity to challenges with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) (17) or β-sitosterol (80). A confounding factor in these effects is that LXRβ is not expressed in DA neurons. Thus, LXR appears to influence DA neurons at two levels: survival with age and neurogenesis at E11.5. In both cases, it is not LXRβ in the DA neurons themselves, but in other cells that influence the differentiation of DA neurons. The cells involved during embryonic development are likely radial glia, but the specific cells responsible for the loss of DA neurons in adult mice with age remain to be determined. It may be that multiple LXR-regulated cells and factors, including cholesterol accumulation, microglial activation, astrogliosis, or a dysfunction of the choroid plexus, influence the survival of DA neurons.

TH is also essential for the differentiation of DA neurons (98), but in this context, it is evident that TRα1 in precursor cells, rather than in DA neurons, is responsible (99). The transcription factor required for embryonic ventral midbrain neural stem cells (NSCs) to differentiate into DA neurons is Otx2. TRα1 is coexpressed with Otx2 in cultured ventral midbrain NSCs. Otx2, in turn, induces a number of other factors, including Neurogenin 2 (Ngn2) and Nurr1 (also known as nuclear receptor 4A2, NR4A2).

Currently, the distinct roles of LXR and TH have not been fully defined. Published data indicate that the functions of TH and LXR have been investigated at different stages of differentiation between E11.5 and E13.5. This is a critical period for the differentiation of DA neurons (100), and many steps in DA neuronal differentiation occur before E13.5. Until more detailed timed studies are conducted, it is not possible to separate the roles of TH and LXR in the differentiation of DA neurons.

Of key interest to human disease is the late-onset of loss of DA neurons in LXR$\beta^{-/-}$ mice. Since Parkinson's disease is a late-onset condition, the LXR$\beta^{-/-}$ mice may provide valuable insights into this disease.

TRs in Cerebellum

Ishii *et al*. summarized that various mouse models have been used to evaluate the effects of TH on cerebellar development, reveling extensive abnormalities that result in an ataxic phenotype (101). The postnatal

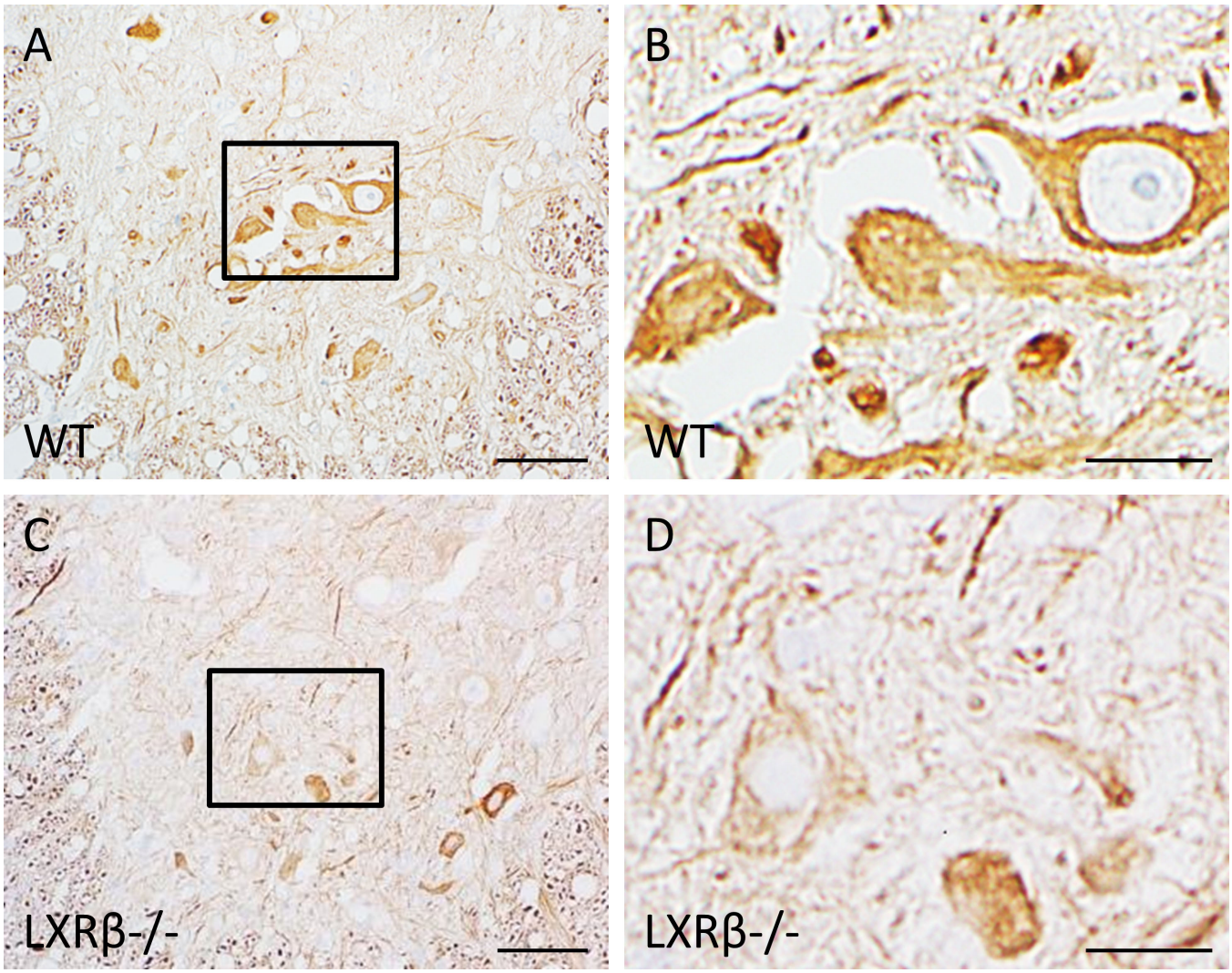

Figure 3. The number of motor neurons in the ventral horn of the spinal cord of LXR$\beta^{-/-}$ mice is less than that of WT mice. Neurofilament staining. 11 months of age. Scale bars: A and C, 50 μm; B and D, 20 μm.

defects observed in the cerebellum of hypothyroid mice are recapitulated in mice heterozygous for a dominant-negative mutation in the TRα1 receptor (102, 103). This mutation primarily affects the differentiation of Purkinje cells and Bergmann glia.

LXRs and TRs in Development of the Dentate gyrus

The dentate gyrus (DG) of the hippocampus plays a prominent role in learning, memory, and emotion. The subgranular zone (SGZ) of the hippocampal DG is one of the stem cell–containing niches in the adult mammalian brain (104). The permissive milieu of the SGZ allows NSCs to proliferate while promoting the specification and differentiation of dentate granule neurons. In the DG of LXR$\beta^{-/-}$ mice, there is hypoplasia and abnormalities in progenitor cell formation and granule cell differentiation, resulting in autistic-like behavior (105). In GW3965-treated 3xTg-AD mice, the number of stem cells and proliferating cells increased in the SGZ (106). Furthermore, LXR activation ameliorated learning and memory impairments by promoting neuronal survival, NSC proliferation, and neurogenesis in the DG in different animal models (107, 108).

Hypothyroidism results in reduced hippocampal volume in adults (109). THs affect neurogenesis in the DG of adult rats (110) and are essential for preserving nonproliferative cells involved in adult neurogenesis (111). In 2024, Valcárcel-Hernández *et al*. provided an excellent summary of THs in the SVZ (subventricular zone) lining the lateral ventricles, the hippocampal SGZ, and the hypothalamus, controlling the generation of new neuronal and glial progenitors from NSCs, as well as their final differentiation and maturation programs (112).

LXRs and TRs in Alzheimer's Disease

AD, the most common cause of dementia globally, is a progressive neurodegenerative disease characterized by initial memory impairment and cognitive decline, with the presence of amyloid plaques and neurofibrillary tangles being crucial for a pathological diagnosis (113). Both TH and LXR signaling have been implicated in AD (Figure 4). As discussed above, LXR signaling is intricately linked to TH levels. Because LXR inhibits deiodinases, a reduction in LXR signaling should be associated with higher levels of TH. Therefore, the reduced signaling of both TH and LXR in AD is puzzling.

Several studies have investigated the association between thyroid dysfunction and dementia risk (114–116). Meta-analyses revealed a higher prevalence of hypothyroidism in AD, but the authors cautioned that the finding could not distinguish whether hypothyroidism is a risk factor for or a consequence of AD (117). One of the most beneficial effects of TH in AD is its effects in repression of microglial immune responses (118). However, no definitive link between thyroid dysfunction and AD has been established (119–121).

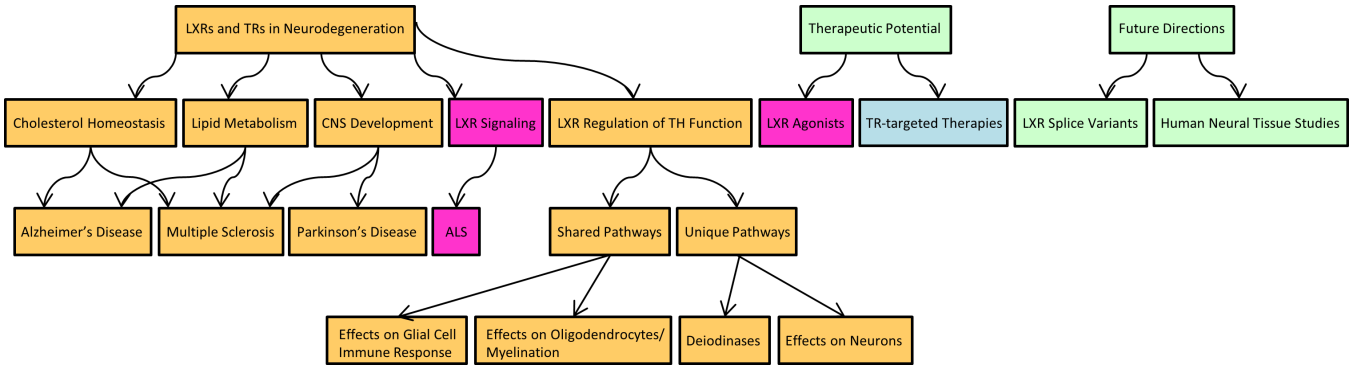

Figure 4. Unraveling the complex roles of LXRs and TRs in neurodegenerative diseases. This diagram depicts the intricate biology of LXRs and TRs and their roles in neurodegenerative diseases. At the heart of our conceptual framework is how these receptors influence key processes in the brain—from managing cholesterol levels to shaping brain development. We can see how their actions ripple out to affect various neurodegenerative conditions, including Alzheimer's and Parkinson's diseases, as well as ALS and multiple sclerosis. An interesting twist revealed by the diagram is that LXRs actually help regulate thyroid hormone function, adding another layer of complexity. We have used different colors to highlight which processes are specific to LXRs (in pink) or TRs (in light blue), while shared pathways are shown in orange. Looking to the future, we have included promising therapeutic approaches and exciting new research directions in light green. This visual framework captures our current understanding and also points to where the next chapters in this emerging scientific narrative might lead us.

In the context of LXR and AD, activation of LXR has been considered a therapeutic strategy (11, 71, 73, 122–124) for several reasons: 1) ApoE, an LXR-induced gene, promotes the proteolytic degradation of Aβ in various AD animal models (106, 125–128), thereby reducing brain Aβ burden; 2) Inhibition of neuroinflammation (129, 130), including the activation of microglia and astrocytes (131, 132); 3) LXR ligands ameliorate the impairments in synaptic plasticity (133, 134); 4) Genetic loss of LXRs in APP/PS1 transgenic mice results in increased amyloid plaque burden (135); 5) T0901317 has beneficial effects on memory by enhancing brain cholesterol turnover in APPSLxPS1mut mice (136); 6) In APP/PS1 mice, LXR agonists exert beneficial effects in ameliorating memory impairment by elevating levels of ApoE and ABCA1, reducing the expression of proinflammatory genes, and decreasing Aβ aggregation (137–139); 7) Activation of LXR with the agonist T0901317 decreased BACE1 expression and activity by lowering membrane cholesterol levels (140); 8) DMHCA, a partial LXR agonist, prevented memory decline and significantly decreased hippocampal Aβ oligomers without affecting plasma lipid levels (141).

One gene that is upregulated by both LXR and TRβ is the seladin-1 (selective AD indicator-1), encoded by the 3beta-hydroxysterol-Delta24 reductase (DHCR24). DHCR24 is a crucial enzyme in cholesterol synthesis, catalyzing the conversion of desmosterol into cholesterol and lanosterol to 24,25-dihydrolanosterol. Both LXRα and TRβ upregulate the transcription of DHCR24 (142–144), suggesting it may be a common gene linking TR and LXR to AD.

LXRs and TRs in Demyelinating Diseases

Since cholesterol is an essential component of all cell membranes and is particularly enriched in myelin membranes, it is not surprising that cholesterol metabolism is involved in the processes of demyelination and remyelination (145). Oligodendrocytes are the cells in the brain responsible for myelination (146). Both LXRs and TRs are critical for promoting and maintaining myelination (147, 148). Even before myelin synthesis occurs, both receptors are needed for the differentiation of oligodendrocytes. LXRβ regulates the number of oligodendrocyte by driving radial glial cells in the dorsal cortex to become oligodendrocyte progenitor cells (149). Meanwhile, TH is required for the terminal differentiation of oligodendrocyte precursor cells into myelinating oligodendrocytes by inducing rapid cell-cycle arrest and transcription of prodifferentiation genes (150, 151).

Therefore, it is not surprising that the knockout of LXRs in mice results in abnormal myelination and a reduction in the size of myelinated axon in the mouse brain (70, 152, 153). As described above, LXR has widespread functions in the body, and inactivation of LXR leads to multiple organ dysfunction in mice. If LXRs have similar roles in humans and mice, it is difficult to imagine a human surviving with a defective LXR gene without severe defects in lipid homeostasis, vascular disease, and immune and neuronal dysfunction. A mutation in LXRα (p.Arg415Gln) has been reported to be responsible for familial developing progressive MS (154), but the association between the LXRα mutation and MS could not be confirmed by the International MS Genetics Consortium (IMSGC) patient collection (155). Before this issue can be fully resolved, it is essential to examine the function of the LXRα with the (p.Arg415Gln) mutation to determine whether it functions as a normal LXRα and whether the LXR mutation simply segregates with another gene responsible for the MS phenotype.

Martin-Gutierrez *et al*. reported that LXR-mediated lipid metabolism pathways were dysregulated in T cells from patients with relapsing-remitting MS (RRMS) pathology, potentially contributing to RRMS pathogenesis (156). The study shows that LXR regulates T cell function by regulating glycosphingolipid and cholesterol metabolism, although the specific defect in LXR in T cells that could cause RRMS remains undefined.

MS is an autoimmune disease (78, 157, 158) thought to be due to T-cell reactions to antigens associated with myelin, such as myelin basic protein and myelin oligodendrocyte glycoprotein. In chronic demyelinating inflammatory disease models, TH restores normal levels of myelin basic protein mRNA and protein (159, 160) and promotes the differentiation of oligodendrocyte progenitor cells, improving remyelination through TRβ-mediated T3 effects (161).

T4 activates oligodendrocyte precursors and increases the content of myelin-forming proteins and NGF in the spinal cord during experimental allergic encephalomyelitis (162). Studies using the TRβ-selective agonist Sobetirome (GC-1) have found that it promotes remyelination, enhances oligodendrocyte proliferation, and protects against oligodendrocyte death (163–166).

In addition to its effects on oligodendrocytes, another mechanism through which LXR signaling repairs demyelination damage is by acting on microglia/macrophages, inhibiting the inflammatory response and providing a supportive environment for oligodendrocyte differentiation and myelination (167), while also promoting the phagocytic clearance of myelin debris and cholesterol (168). LXR agonists may be useful in healing white matter injury, as LXR ligands have been shown to induce oligodendrogenesis in rodent injury models (169, 170). However, the challenge of limiting LXR action to the targeted area must first be addressed.

Concluding Remarks

The aim of this review was to analyze the roles of LXRs and TRs in neurodegenerative diseases (Figure 4). A review of the literature clearly shows that these two receptors work together to regulate cholesterol homeostasis, and dysregulation of cholesterol homeostasis is a common factor in neurodegenerative diseases. Due to their widespread effects

throughout the body, it is unlikely that generalized dysfunction of either receptor would lead to selective degeneration of certain neurons without causing other significant defects in the body. One possibility that has not yet been addressed is the existence of LXR splice variants that are selectively expressed in the CNS, and it may be dysregulation of these splice variants that contributes to neurodegenerative diseases. Multiple splice variants of both LXRα and LXRβ have been reported (171), but their roles in disease have not yet been investigated. Additionally, the differences in the genomic and physiological functions of nuclear receptors between humans and rodents cannot be ignored, highlighting the need for more research on nuclear receptor signaling in humans or nonhuman primate. In conclusion, it will be crucial to study nuclear receptors, including LXRs and TRs, by investigating their splice variants and examining neural tissues from patients with neurodegenerative diseases.

Author Disclosures

The authors declare no conflicts of interest.

Author Contributions

J-ÅG, MW, and XS conceived the manuscript topic, edited and organized the final draft. XS wrote the first draft of the manuscript and prepared the figures. All authors revised the final manuscript and approved the final version.

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