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Liver X receptors and cholesterol metabolism: role in ventral midbrain development and neurodegeneration

Spyridon Theofilopoulos and Ernest Arenas*

Address: Laboratory of Molecular Neurobiology, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm SE-17177, Sweden

* Corresponding author: Ernest Arenas (ernest.arenas@ki.se)

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Abstract

The development of the ventral midbrain is orchestrated by a number of cell-extrinsic and -intrinsic factors that control critical processes, such as the patterning of the neural tube along the main body axis and the specification of diverse neuronal cell types in distinct positions of the neural tube. Subsequently, the regulation of neurogenesis and survival— acquire particular relevance in order to define the final size of diverse neuronal populations. In a series of studies during the last few years, we have identified liver X receptors (LXRs) as critical regulators of ventral midbrain development. Moreover, specific cholesterol derivatives present in the midbrain or in the cerebrospinal fluid were identified as LXR ligands, capable of specifically and selectively regulating neurogenesis and the survival of distinct neuronal populations, including midbrain dopamine neurons. These studies have shown that cholesterol derivatives are an entirely new class of factors capable of regulating both neuronal survival and neurogenesis, thus providing a direct link between cholesterol metabolism and brain development. In addition, LXRs and cholesterol metabolism were found to play a critical role in regulating the balance between neuronal survival and death in diverse midbrain neuronal populations. In this review, we will focus on these two aspects and on the possible role of cholesterol metabolism and LXRs in neurodegeneration.

LXRs and oxysterols

LXRs (LXRα/NR1H3 and LXRβ/NR1H2) are members of the nuclear receptor superfamily that heterodimerize with retinoid X receptors and are activated by specific cholesterol derivatives that function as endogenous ligands [1–12]. One well known set of ligands are oxysterols, oxidized metabolites of cholesterol that are present in very low concentrations in mammalian systems and are always accompanied by a high excess of cholesterol. LXR ligands with a hydroxyl, oxo, epoxide, or carboxylic group on the C-17 steroid side chain of cholesterol have been shown to regulate genes involved in cholesterol turnover [1,3,8,10–12]. The efficiency of LXR ligands varies depending on the target cell type, tissue, developmental stage and species. In addition to the aforementioned ligands, synthetic non-steroidal LXR ligands with higher potency and efficiency, such as T0901317 and GW3965, have been developed.

It is currently thought that a number of effects previously attributed to cholesterol are actually mediated by oxysterols, since their effects are more potent and they have a greater capacity to cross membranes compared with cholesterol [13]. However, transgenic mouse models with overexpression or deletion of enzymes involved in the synthesis of oxysterols, such as sterol 27-hydroxylase (*CYP27* [14,15]), cholesterol 24-hydroxylase (*CYP46A1* [16,17]) or oxysterol 7a-hydroxylase (at the *Cyp7b1* locus [18]), result in only modest changes in the levels of cholesterol and cholesterol metabolites, suggesting that alternative metabolic pathways or

ligands compensate for such defects. Deletion of three oxysterol-biosynthetic enzymes in triple-knockout mice (*Cyp46a1*$^{-/-}$, *Ch25h*$^{-/-}$, *Cyp27a1*$^{-/-}$) altered the biosynthesis of three oxysterols (24(S)-hydroxycholesterol, 25-hydroxycholesterol, and 27-hydroxycholesterol) and impaired the transcription of some LXR target genes, such as *LPL*, *ABCG5*, and *ABCG8* after cholesterol feeding [19]. Other LXR ligands such as 24(S), 25-epoxycholesterol (24,25-EC) were not impaired and could compensate for the remaining LXR signaling in these mice. However, the complexity of this mouse model has made it difficult to interpret the results and to evaluate the regulatory role of these oxysterols under physiological conditions.

The best known functions of Lxrs are to regulate lipid metabolism and homeostasis [8,10–13,20–22], increase cholesterol efflux from cells [8,23,24], and protect from cholesterol overload and toxicity [23,25]. Accordingly, direct LXR target genes encode for ATP-binding cassette (ABC) transporters (ABCA1 and ABCG1/5/8), apolipoproteins (E, C1, C2, C4, and D), cytochrome P450 7A1 (in rodents but not in humans), and enzymes involved in lipogenesis such as SREBP1c, FAS, and stearoyl-CoA desaturase-1 (for review, see [12]).

In the last decade, new functions of Lxrs and their ligands have been described. These include the regulation of inflammation [9,26,27] and different aspects of the immune response [27–29], including the regulation of the balance between cell survival and death in macrophages [30]. Accordingly, endogenous LXR ligands have been identified in multiple tissues. For instance, 27-hydroxycholesterol is present in macrophages [31], 22(R)-hydroxycholesterol (22-HC) in steroidogenic tissues [32,33], and 24(S)-hydroxycholesterol (24(S)-HC) in plasma and adult brain [3]. Other ligands such as 24,25-EC are present in the liver [1] and the developing ventral midbrain (VM) [34]. More recently, cholestenoic acids in adult human cerebrospinal fluid (CSF) have also been identified as endogenous LXR ligands [35], suggesting novel functions for LXR ligands in the developing and the adult brain.

Specific cholesterol metabolites regulate neurogenesis or survival (or both) in selected midbrain neuronal types via LXRs

The developing VM arises from ventral progenitor cells flanking the ventricles, which give rise to distinct neuronal populations that organize in discrete nuclei. The best-characterized neurons in the VM are the dopaminergic (DA) neurons of the substantia nigra and ventral tegmental area. Less is known about the cues controlling the development of other nuclei in the VM, such as the oculomotor nucleus (OM), the trochlear nucleus, and the red nucleus (RN). The induction of these cell types depends on the expression of fate-determining transcription factors (TFs) that are regulated by both cell-extrinsic and -intrinsic signals along the dorso-ventral and anterior-posterior axis of the neural tube [36–38]. Subsequently, the emergence of DA, RN, and OM neurons in the VM and the number of cells in each nuclei is critically regulated by two processes: neurogenesis and survival. Several classes of molecules have been previously reported to regulate these two processes, such as proneural basic helix-loop-helix genes such as Mash1 and Ngn2, which regulate VM neurogenesis [39], and neurotrophic factors such as glial-derived neurotrophic factor [40], which regulate neuronal survival during VM development.

In the developing mouse VM, Lxrs have been shown to regulate the balance between neurons and glia during early midbrain development [41]. Indeed, the number of progenitors undergoing neurogenesis in *Lxr*$\alpha\beta^{-/-}$ mice is reduced, resulting in a predominant impairment of VM neurogenesis in the midline and an accumulation of progenitors and radial glia cells [41]. In addition, deletion of Lxrs reduced cell cycle progression at G_2/M, decreased cell cycle exit, reduced the levels of Mash1 and particularly Ngn2, a basic helix-loop-helix transcription factor (TF) required for midbrain DA neurogenesis [39], and resulted in a decreased number of both DA and oculomotor neurons in the developing midbrain. In support of these findings, specific oxysterol biosynthetic enzymes (such as oxidosqualene cyclase) are expressed at high levels in oculomotor neurons and at sites of DA neurogenesis in the VM [41]. Moreover, overexpression of Lxrs or their activation by classic oxysterol ligands increased the number of midbrain DA neurons derived from mouse embryonic stem (ES) cells and in VM progenitor cultures [41].

More recently, specific endogenous midbrain LXR ligands have been identified as promoters of DA or RN neurogenesis and survival [34]. Cholic acid (CA) has been identified as an entirely new endogenous LXR ligand and 24,25-EC as the most abundant and potent endogenous LXR ligand in the developing midbrain. The activity of these two ligands was directed toward two distinct midbrain neuronal populations. Whereas CA increased the number of RN neurons by promoting neuronal survival and neurogenesis, 24,25-EC specifically promoted DA neurogenesis in midbrain progenitor cells. The molecular mechanism by which endogenous LXR ligands selectively regulate neurogenesis or survival in specific neuronal populations is currently under investigation.

Nevertheless, the function of Lxrs is not limited to the developing VM. Deletion of Lxrα and Lxrβ results in lipid accumulation in astrocytes and ventricular/periventricular cells during aging [42]. The progressive accumulation of lipids in the brain and the abnormal blood-brain barrier of adult Lxr double-knockout (*Lxr*$\alpha\beta^{-/-}$) mice have been reported to contribute to lipid toxicity, increased reactive microglia, astrogliosis, and degeneration of adult spinal cord motor neurons and midbrain DA neurons [42–44]. These results indicate that Lxrs play an important role not only in VM development, by promoting neurogenesis and survival, but also in the adult brain, by regulating the maintenance of both midbrain DA neurons and motor neurons.

Additionally, we have found that oxysterols promote the DA differentiation of human cells. LXR ligands, such as 22-HC or 24,25-EC, reduced progenitor proliferation and promoted DA neurogenesis from mouse or human ES cells, resulting in an increased number of mature DA neurons [34,41]. These results indicate that LXR ligands may find an application to improve current human ES cell replacement strategies for neurodegenerative diseases affecting midbrain DA neurons, such as Parkinson's disease (PD).

Do altered levels of cholesterol metabolites lead to the degeneration of midbrain neurons?

Since LXR ligands regulate not only neurogenesis but also neuronal survival, it is possible that changes in cholesterol metabolism impair neuronal survival in the adult brain. Evidence in favor of this possibility comes from the recent analysis of two neurological diseases: hereditary spastic paresis type 5 (SPG5) (characterized by lower extremity weakness, spasticity, and in some cases mental retardation, cerebellar ataxia, optic, and peripheral neuropathy) and cerebrotendinous xanthomatosis (CTX) (characterized by progressive cerebellar ataxia, juvenile cataracts, diarrhea, neurological deficits, and tendinous xanthomas in the cerebellum). These diseases result from mutations in CYP7B1 or CYP27A1, respectively, two enzymes involved in the synthesis of cholestenoic acids, intermediaries between cholesterol and bile acids. Analysis of plasma or CSF of patients with CTX and SPG5 revealed alterations in cholestenoic acid levels [35]. Some of these activated Lxrs, but not other nuclear receptors, and regulated Islet-1, a TF required for motor neuron development. One cholestenoic acid that was found at high levels in patients with SPG5, 3β-hydroxycholest-5-en-26-oic acid (3β-HCA), caused motor neuron cell loss, whereas 3β,7α-dihydroxycholest-5-en-26-oic (3β,7α-diHCA), which was found at low levels in patients with CTX or SPG5, promoted motor neuron survival in an Lxr-dependent manner in zebrafish motor neurons and in mouse oculomotor neurons *in vitro* and *in vivo* [35]. These results indicate that specific cholestenoic acids work via Lxrs to regulate the balance between motor neuron survival and death. Moreover, our findings suggest that the modulation of cholestenoic acid biosynthesis or metabolism (or both) may contribute to restore the balance between toxic and pro-survival LXR ligands, leading to potential treatments for diseases involving motor neuron degeneration.

Are statins of therapeutic interest in neurodegenerative diseases?

One way of modifying cholesterol metabolism and decreasing possible toxic compounds is by using statins. Statins are a class of drug capable of lowering cholesterol levels by inhibiting 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, an enzyme that plays a central role in the production of cholesterol in the liver. Increased cholesterol levels have been associated with cardiovascular disease, and statins have been found to prevent cardiovascular diseases in those who are at high risk [45]. However, the effects of statins in patients with neurodegenerative diseases, such as PD, are less clear [46]. Interestingly, short-term statin administration in the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) model of PD either showed neuroprotective effects [47] or failed to show neuroprotection [48,49]. However, administration of statins for a longer period (3 to 8 weeks) induced anti-inflammatory and neuroprotective effects on substantia nigra DA neurons both in the 6-OHDA model of PD [50,51,52] and in transgenic mice overexpressing α-synuclein [53]. Additionally, recent studies have indicated that statins reduce the risk of PD [54,55] and that continuation of statin treatment decreased the incidence of PD compared with discontinuation of the treatment [56].

Statins have been used in other neurodegenerative diseases, such as Alzheimer's disease (AD), which also show alterations in brain oxysterol levels, such as increased 27-hydrocycholesterol and decreased 24-hydrocycholesterol [57]. Interestingly, simvastatin was found to enhance learning and memory in amyloid precursor protein (APP) mice with the Swedish mutation [58] and to promote adult hippocampal neurogenesis in rodents [59]. Two retrospective studies suggested that statins reduce the incidence of AD [60] and the prevalence of dementias [61]. However, several studies (reviewed in [62]), including a prospective study [63], have shown no significant effect of statins on cognitive function or disability. Thus, further studies are required in order to unequivocally assess the usefulness of statins in AD.

In experimental autoimmune encephalitis (EAE), an animal model of multiple sclerosis (MS), statins have shown potent anti-inflammatory effects [64] and were able to attenuate the acute phase of disease and prevent relapse [65]. Moreover, in an open-label clinical trial on patients with relapsing-remitting MS, treatment with statins (simvastatin 80 mg/kg for 4 to 6 months) during the active phase of disease was able to decrease the number of gadolinium-enhancing lesions identified by nuclear magnetic resonance (NMR) [66]. More recently, a double-blind placebo-controlled clinical trial showed that simvastatin (80 mg/kg) reduced the annualized rate of whole brain atrophy by 43% as assessed by NMR, although improvement of disability was unclear [67]. Although these results are very promising, it should be considered that prolonged high doses of statins may affect remyelinization and axonal regeneration, two processes that also require cholesterol.

In sum, statins seem to exert some neuroprotective and anti-inflammatory effects that may be of interest for the treatment for neurodegenerative diseases, but excessively high levels may be detrimental. In addition, it should be noted that conclusive proof for the use of statins as therapeutic tools in these diseases is still missing. One of the problems of statins is that their effects on cholesterol metabolism are very broad, making it difficult to identify the metabolites and the molecular mechanisms responsible for the observed effects as well as the development of more specific drugs. One alternative approach to statins may be inhibitors working in specific branches of cholesterol metabolism where it may be possible to decrease the levels of toxic metabolites or increase those promoting survival, neurogenesis, or neuroprotection. For instance, in the future, it may be interesting to develop enzyme inhibitors capable of increasing the levels of cholesterol metabolites with beneficial effects, such as 24,25-EC for midbrain DA neurons [36] or 3β,7α-diHCA for motor neurons [35].

Are LXR ligands of therapeutic interest in neurodegenerative diseases?

Several studies have investigated the potential therapeutic use of natural or synthetic LXR ligands in neurodegenerative disorders, such as AD. A cholesterol-rich diet, for instance, can increase the risk of developing AD, and patients with atherosclerotic heart disease have a higher incidence of AD. Alterations in LXR target genes, such as specific apolipoprotein E (ApoE) variants, are considered to be the main risk factor for AD [68–71]. Moreover, decreased expression levels of another LXR target gene, 3-betahydroxysterol delta-24 reductase (DHCR24/Seladin), an enzyme that catalyzes a crucial step in the formation of cholesterol from desmosterol, are found in patients with AD [72–74]. In agreement with these data, deletion of either LXRα or LXRβ, which leads to increased levels of cholesterol, results in a marked increase in amyloid-β (Aβ) deposition and AD-like pathology in the APP/presenilin-1 (PS1) transgenic mouse model of AD [75,76]. Conversely, administration of the synthetic LXR agonist T0901317 to the Tg2576 mouse model of AD decreased Aβ42 levels while increasing ABCA1 and ApoE in the hippocampus [77,78]. Similarly, the LXR agonist TO901317 facilitated Aβ and cholesterol efflux from neural cells, leading to elevated levels of ApoE, cholesterol, Aβ40, and Aβ42 in the CSF in only 3 days and a significant reduction of soluble brain Aβ40 after 6 days of treatment [77]. TO901317 also reduced protein aggregation and Aβ load in two transgenic models of AD by mechanisms involving not only extracellular cholesterol transport by ABCA1 but also lipidation of ApoE and degradation of Aβ by microglia [77,79]. Moreover, a recovery of cognitive functions and contextual or spatial memory has been reported in different transgenic mice, including APP23, Tg2576, and APP/PS1 mice [76–78,80,81]. These results indicate that LXR is an attractive pharmacological target in AD and that its activation by LXR ligands may inhibit APP processing and accelerate Aβ clearance in AD.

LXRs and their ligands are also known to act as potent inhibitors of inflammation in the brain by working at different levels, (a) reducing the proliferation and migration of T lymphocytes [82,83], a cell type that is recruited to the substantia nigra in patients with PD [84]; (b) attenuating the inflammatory response of glia by reducing the expression of inflammatory mediators as well as cytokines and chemokines—interleukin-1 beta (IL-1β), IL-6, CCL2, 5, 7, and CXCL10—that recruit and activate inflammatory cells [75]; and (c) reducing the recruitment of microglia without impairing their phagocytic activity [75]. Indeed, LXR ligands suppressed the production of pro-inflammatory factors in the APP/PS1 model of AD [81] and attenuated cellular inflammation and the expression of major histocompatibility class II antigens on microglia in an EAE model of MS [82,84]. Moreover, deletion of *lxrα/β* in EAE mice resulted in more severe demyelination and inflammatory infiltration in the spinal cord than in wildtype (WT) mice [85]. Similarly, LXR ligands have been found to prevent the loss of midbrain DA neurons and motor neurons in *Lxrβ*$^{-/-}$ mice, reduce the formation of ubiquitinated intracellular aggregates in spinal cord motor neurons, and decrease the recruitment of microglia to the substantia nigra [44]. Moreover, Dai and colleagues [86] have shown that *Lxrβ*$^{-/-}$ mice are more vulnerable to MPTP-induced DA neuron loss and that GW3965 prevents the loss of substantia nigra DA neurons and of

DA fibers projecting to the striatum in MPTP-treated WT mice. Since LXRβ was not expressed in adult substantia nigra neurons but rather in the microglia and astroglia, it is thought that the beneficial effects of LXR ligands are related to the modulation of the cytotoxic functions of microglia and to the anti-inflammatory actions of LXR.

In summary, studies examining animal models of disease collectively suggest that LXR agonists may be effective in the treatment of AD, by additionally reducing amyloid aggregates, and in the treatment of several other neurodegenerative diseases, such as MS and PD, by reducing neuroinflammation. However, not much information is currently available about the expression of LXR ligands and receptors in the human adult brain or their alterations in patients with these neurodegenerative diseases. Additionally, a better understanding of the mechanism of action of distinct LXR ligands and better models of human disease are required in order to improve and develop LXR ligands or activators as therapeutic tools for neurodegenerative diseases. Future work in the field undoubtedly will focus on these issues.

Abbreviations

22-HC, 22(R)-hydroxycholesterol; 24,25-EC, 24(S), 25-epoxycholesterol; Aβ, amyloid-β; AD, Alzheimer's disease; APP, amyloid precursor protein; ApoE, apolipoprotein E; CA, cholic acid; CSF, cerebrospinal fluid; CTX, cerebrotendinous xanthomatosis; DA, dopaminergic; EAE, experimental autoimmune encephalitis; ES, embryonic stem; LXR, liver X receptor; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; NMR, nuclear magnetic resonance; OM, oculomotor nucleus; PD, Parkinson's disease; PS1, presenilin-1; RN, red nucleus; SPG5, spastic paresis type 5; TF, transcription factor; VM, ventral midbrain; WT, wildtype.

Disclosures

The authors declare that they have no disclosures.

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