Lipid Metabolism and Neuroinflammation in Alzheimer's Disease: A Role for Liver X Receptors

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Liver X receptors (LXR) are nuclear receptors that have emerged as key regulators of lipid metabolism. In addition to their functions as cholesterol sensors, LXR have also been found to regulate inflammatory responses in macrophages. Alzheimer's disease (AD) is a neurodegenerative disease characterized by a progressive cognitive decline associated with inflammation. Evidence indicates that the initiation and progression of AD is linked to aberrant cholesterol metabolism and inflammation. Activation of LXR can regulate neuroinflammation and decrease amyloid-β peptide accumulation. Here, we highlight the role of LXR in orchestrating lipid homeostasis and neuroinflammation in the brain. In addition, diabetes mellitus is also briefly discussed as a significant risk factor for AD because of the appearing beneficial effects of LXR on glucose homeostasis. The ability of LXR to attenuate AD pathology makes them potential therapeutic targets for this neurodegenerative disease. (***Endocrine Reviews*** **33: 715–746, 2012)**

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I. Introduction

A. Background of Alzheimer's disease (AD)

Alzheimer's disease (AD) was first described by Alois Alzheimer in 1907. It is the most common form of dementia characterized by an initial subtle and poorly recognized memory loss and increasingly severe dementia (1). With the rising number of patients worldwide and the increasing burden on society, AD represents a major public health issue. In all AD cases, only 5% or less are familial with an early onset. Most patients are sporadic with a late onset and without known causes [sporadic AD (SAD)]. The two core pathological hallmarks of AD are abnormal extraneuronal deposition of amyloid-β peptides (Aβ) in senile plaques and intraneuronal accumulation of hyperphosphorylated tau in neurofibrillary tangles (2). For

Abbreviations: Aβ, Amyloid-β peptides; ABC, ATP-binding cassette; AD, Alzheimer's disease; apoE, apolipoprotein E; APP, amyloid precursor protein; BBB, blood-brain barrier; CH25H, cholesterol 25-hydroxylase; ChREBP, carbohydrate response element-binding protein; CNS, central nervous system; CoA, coenzyme A; Cyp7a1, cytochrome P450 7a1; FA, fatty acids; fAβ, fibrillar amyloid β-peptide; FAS, FA synthase; FDFT1, farnesyl diphosphate farnesyl transferase 1; FoxO1, Forkhead box class O 1; GSK, glycogen synthase kinase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDLR, LDL receptor; LPS, lipopolysaccharide; LRP1, LDLR-related protein 1; LXR, liver X receptor; LXRE, LXR-responsive element; ME.1, multienhancer 1; N-CoR, nuclear receptor corepressor; NF-κB, nuclear factor κB; NPC1, Niemann-Pick type C1; 24OHC, 24(S)-hydroxycholesterol; PI3K, phosphoinositide 3-kinase; PKB, protein kinase B; PPAR, peroxisome proliferator-activated receptor; RCT, reverse cholesterol transport; ROS, reactive oxygen species; RXR, retinoid X receptor; SAD, sporadic AD; SREBP, sterol regulatory element-binding protein; SUMO, small ubiquitin-like modifier; T2DM, type 2 diabetes mellitus; TG, triglyceride; TLR, Toll-like receptor; Wnt, wingless.

many years, the precise relationship between these two pathological AD hallmarks and whether Aβ or tau abnormalities are the primary cause driving AD pathogenesis issues have been much debated, especially for SAD. The amyloid hypothesis was first formulated in the early 1990s, particularly based on genetic studies (1, 3). This hypothesis proposed that deposition of Aβ is the prime phenomenon driving AD pathogenesis. Other disease processes and clinical features, including the formation of tau protein-containing neurofibrillary tangles, have been proposed to result from the abnormal Aβ production and clearance. It has now been suggested that in early-onset AD, elevation of Aβ drives other disease features, including tau hyperphosphorylation. In late-onset AD, a dual pathway model has been proposed. Based on these hypotheses, a common upstream molecular defect is thought to lead to Aβ elevations and tau hyperphosphorylation in parallel, but via independent mechanisms (4).

Full-length amyloid precursor protein (APP) is a glycoprotein that is ubiquitously expressed in human tissues. It is localized at the plasma membrane as well as in several organelles, such as mitochondria, endoplasmic reticulum, and Golgi apparatus. Aβ is a sequentially cleaved product of APP by β- and γ-secretases, which leads to the formation of nonsoluble, deleterious Aβ (5). Full-length APP can also undergo alternative processing by α-secretase, releasing a soluble fragment extracellularly, which precludes Aβ formation. There are mainly two variants of the Aβ peptide, $A\beta_{1-40}$ and $A\beta_{1-42}$. Of the two, $A\beta_{1-42}$ is thought to be the most pathogenic and have the highest propensity for aggregation. The extracellular Aβ eventually generates fibrils and deposits as plaques. Intracellular Aβ oligomers and extracellular Aβ plaques are key players in the progression of SAD. Abnormal elevations in Aβ result in synaptic loss and neuronal death. Excessive generation and accumulation of Aβ peptides in neurons is believed to initiate the pathological cascade characteristic of AD (6, 7). Decreasing its level has thus been a target that stimulated drug development. Several potential therapies aim at reducing $A\beta_{1-42}$ by potentiation of α-secretase (8), inhibition of β-secretase (9, 10), modulation of γ-secretase activity (11), immunization with Aβ (12), or the use of natural antibodies against Aβ.

Tau is a highly soluble cytoplasmic microtubule-associated protein. Its main role is to participate in axonal transport and neurotransmission (13). Tau protein undergoes different posttranslational modifications, including phosphorylation, glycosylation, ubiquitinylation, *etc*. The formation of hyperphosphorylated aggregated insoluble tau results in the loss of axonal transport in a number of taupathies including AD. Much effort has been devoted to develop compounds that can interfere with tau aggregation. An interesting approach is to inhibit the kinases responsible for tau hyperphosphorylation. Among the multiple phosphokinases found in that respect, glycogen synthase kinase (GSK)-3β has emerged as the potential target to reduce tau hyperphosphorylation therapeutically (14, 15). Results of a very recent study also revealed that tau immunotherapy is effective at preventing the pathology due to buildup of intracellular tau and should be considered as an approach for the treatment of AD (16).

In addition to its two core pathological hallmarks, AD is associated with microglia-mediated inflammation and dysregulated lipid homeostasis and glucose metabolism. A large body of evidence suggested the use of nonsteroidal antiinflammatory drugs for the prevention of AD (17). However, many of the latter failed to slow the progression of cognitive decline in patients with mild to moderate AD or cannot be used for treatment, as in the case of indomethacin, due to their prevalent gastrointestinal side effects (18). Cholesterol-lowering drugs (statins) (19) and antidiabetic agents (20) have also been tested in clinical trials. At present, all licensed treatments can only at best alleviate symptoms of AD and some are not efficient in the phase III study despite encouraging results in a phase II trial (21). Thus, much work is still needed to improve our understanding of the pathogenesis of AD.

Many factors, including aging, genetics, head injuries, and environmental factors contribute to the development and progression of AD. Aging is the strongest risk factor for AD. The mitochondrion, an organelle that is the major source of reactive oxygen species (ROS) in the central nervous system (CNS), appears to play a role in both AD and brain aging. Mitochondrial dysfunction has been recognized as an early event in AD (22). As an alternative to the amyloid hypothesis, a mitochondrial cascade hypothesis has been proposed for SAD (23–25). According to the hypothesis, mitochondrial function declines with age, which promotes some features of the aging brain including Aβ accumulation. When mitochondrial decline surpasses a threshold, compensatory mechanisms fail, and late-onset AD ensues. In fact, Aβ has a direct interaction with mitochondria (26). Aβ can be imported from endosome, Golgi, and endoplasmic reticulum into mitochondria (27, 28). Accumulation of intraneuronal mitochondrial Aβ triggers mitochondrial dysfunction through a number of pathways such as elevation of ROS production. Mitochondria-derived ROS in turn result in enhanced Aβ level both *in vitro* and *in vivo* and then further impair mitochondrial function (29). This cycle finally induces neuronal toxicity and neuronal death in AD. Eckert and colleagues (30) have also shown the synergistic effects of Aβ and tau in destroying mitochondria by using mice having both Aβ plaque pathology (APP/PS2) and the tangle pathology (pR5).

Established genetic causes of AD include inherited mutations in genes encoding APP, presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*), which are among the causes of familial AD. The neuronal sortilin-related receptor *SORL1* (also known as *LR11* or *SORLA*) is also genetically associated with AD, however, in late-onset AD (31). Moreover, a few potential AD risk genes have been identified, including apolipoprotein E (*apoE*), *GSK-3β* (32), tau, dual-specificity tyrosine-regulated kinase 1A (*Dyrk1a*) (33), translocase of the outer mitochondrial membrane 40 homolog (*Tomm40*) (34), clusterin (*CLU*, also called *APOJ*) (35), phosphatidylinositol-binding clathrin assembly protein (*Picalm*) (36), the bridging integrator1 (*BIN1*) (37), and the complement component (3b/4b) receptor 1 (*CR1*) (35, 36). The identification of these genes may have important roles in drug design.

B. Liver X receptor (LXR) as potential targets for treatment of AD

Among the identified potential risk genes for AD, the ε4 allele of *apoE* is the strongest known genetic risk factor for AD. It is also the only AD risk gene known to be involved in lipid metabolism (38). The primary role for apoE in the CNS is to shuttle cholesterol between cells, which is required for normal cellular and physiological functions. Dysregulation of cholesterol metabolism in the CNS is associated with brain disorders such as Huntington disease (39) and Niemann-Pick type C disease (40). Increasing evidence shows that alterations in cholesterol homeostasis also play an important role in the initiation and development of AD (41, 42). The amount of lipids carried by apoE is a critical determinant of Aβ metabolism. Elevated cholesterol levels may increase the risk of developing AD (43, 44).

ApoE is a direct target of LXR. LXR function as nuclear cholesterol sensors that are activated in response to elevated intracellular cholesterol levels. Activation of LXR promotes cholesterol efflux, induces hepatic lipogenesis, and inhibits inflammation (45). Studies over the past few years have revealed the contribution of LXR genetic variability to the risk of AD (46). Moreover, the activation of LXR modulates the production of inflammatory molecules together with Aβ burden in AD (47, 48). Substantial evidence has indicated the involvement of robust microglia-mediated inflammation in AD patients and animal models. Activated microglia surrounding Aβ plaques express receptors of innate immunity and secrete proinflammatory cytokines. The innate immunity is suggested to be involved in the early stages of pathological cascade and proposed to contribute to the etiology of late-onset AD (49). It has thus been proposed that LXR might be potentially tractable targets for the treatment and/or prevention of AD (50). In this review, we discuss the impact of the LXR pathway on the pathogenesis of AD through modulation of both lipid metabolism and neuroinflammatory signaling. In addition, the potential beneficial role for LXR in regulating glucose homeostasis in AD in the context of diabetes is also discussed.

II. LXR Action in Lipid and Glucose Homeostasis

A. LXR genes

The genes encoding LXR were cloned more than a decade ago (51, 52). LXR were initially discovered as orphan receptors lacking known ligands and functions. They were subsequently identified as the nuclear receptor target of oxysterols, a specific class of oxidized cholesterol derivatives. There are two isoforms of LXR, namely LXRα (also known as NR1H3 and RLD-1) and LXRβ (also known as NR1H2). The human LXRα gene is located on chromosome 11p11.2, and LXRβ is located on chromosome 19q13.3. LXRα and LXRβ have considerable sequence homology and share approximately 78% identity in their amino acid sequence at the DNA- and ligand-binding domains. They can be activated by the same naturally occurring oxysterols, the best studied and most potent of which including 24(S)-hydroxycholesterol, 22(R)-hydroxycholesterol, 24(S),25-epoxycholesterol, and 27-hydroxycholesterol (53, 54). LXRα and LXRβ also have almost identical targets. However, the expression of LXRα and LXRβ differs significantly from tissue to tissue. LXRα is highly expressed in the liver, adipose tissue, adrenal glands, intestine, kidney, and macrophages, whereas LXRβ is ubiquitously expressed. In tissues such as liver, LXRα is the predominant isoform in the regulation of cholesterol metabolism and lipogenesis. In contrast, LXRβ is the main subtype found in pancreatic β-cells, brain, and oocytes (55–57).

LXR reside within the nucleus and form heterodimers with the retinoid X receptor (RXR), a common partner for several nuclear receptors, including the retinoid acid receptor, peroxisome proliferator-activated receptor (PPAR), vitamin D receptor, thyroid hormone receptor, and farnesoid X receptor (58). The LXR/RXR complex can be activated by either an LXR agonist or by 9-*cis*-retinoic acid, a specific endogenous RXR ligand. LXR/RXR heterodimers bind to LXR-responsive elements (LXRE) in the promoter region of target genes, thereby repressing or activating gene expression. The responsive elements generally consist of two direct repeats of a consensus hexameric sequence AGGTCA separated by a 4-nucleotide spacer (DR-4)

Figure 1.

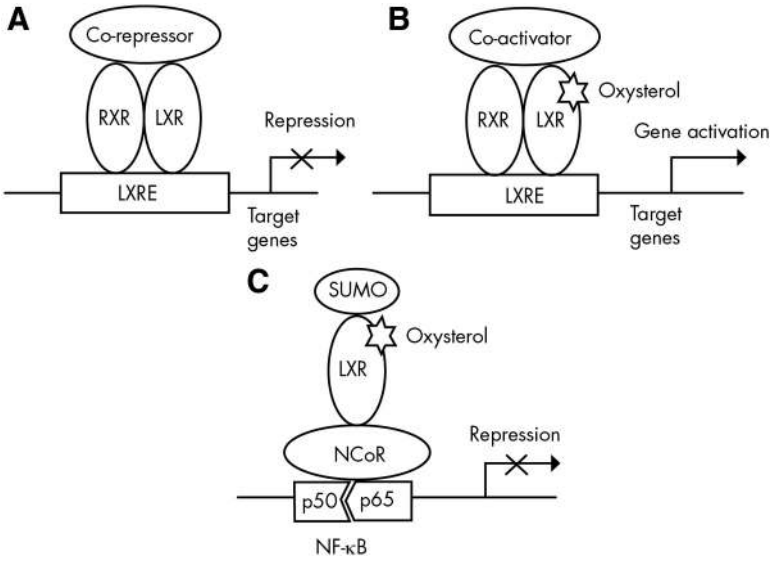

Figure 1. Three models of LXR-regulated gene expression. A, Ligand-independent repression. In the absence of ligands, LXR/RXR heterodimers bind to LXRE and recruit corepressors, which results in the suppressed transcription of target genes. B, Ligand-dependent transactivation. Upon binding with ligands, LXR/RXR heterodimers dissociate with corepressors and recruit coactivators, leading to the stimulation of transcription of target genes regulating insulin sensitivity, RCT, lipid metabolism, glucose homeostasis, *etc.* C, Ligand-dependent transrepression. Ligand binding to LXR results in SUMOylation. The SUMO-LXR complex is then recruited to NF-κB promoter, prevents clearance of corepressor N-CoR, and then inhibits NF-κB-dependent induction of proinflammatory gene expression.

(59). Like most other nuclear receptors that form heterodimers with RXR, the LXR/RXR complex is also associated with corepressors such as silencing mediator for retinoid acid and thyroid hormone receptors (60) or nuclear receptor corepressor (N-CoR) (61) for transcriptional silencing. LXR can regulate gene expression via three different mechanisms as illustrated in Fig. 1. The first model is ligand-independent transcription repression by LXR. The presence of a corepressor is required for the ligand-independent silencing functions of LXR. In the absence of ligand, LXR actively suppress the transcriptional activity of target genes. The second model is the well-established ligand-dependent transactivation. The binding of ligand to LXR induces the dissociation of the corepressors and the recruitment of coactivators, leading to the transcription of target genes. The third model is ligand-dependent LXR transrepression. LXR-dependent transrepression is SUMOylation dependent (62). SUMOylation is a post-translational modification, in which a member of the small ubiquitin-like modifier (SUMO) family is coupled to target proteins to modify their functions. LXR are activated by oxysterols or synthetic agonists in macrophages and conjugated to SUMO2/3. The SUMO2/3-LXR complex is then recruited to nuclear factor κB (NF-κB) promoter, which prevents N-CoR clearance and then inhibits transcription of inflammatory genes that do not contain LXRE, a phenomenon known as transrepression (62, 63).

Studies over the last decade have established the key roles of LXR in lipid metabolism, glucose homeostasis, and inflammatory signaling. Activation of LXR induces the expression of LXR target genes which are involved in cholesterol trafficking and efflux, including ATP-binding cassette (ABC) proteins A1 (ABCA1) and G1 (ABCG1) (64), and apoE, and down-regulates genes involved in cholesterol biosynthesis, including lanosterol 14α-demethylase (*CYP51A1*), and squalene synthase (farnesyl diphosphate farnesyl transferase 1, *FDFT1*) (65). On the other hand, LXR also regulate fatty acid (FA) synthesis-related genes such as sterol regulatory element-binding protein (SREBP)-1c (66), FA desaturase (*FADS*), steroyl-coenzyme A (CoA) desaturase (*SCD*) (67, 68), and FA synthase (*FAS*) (69). The roles of LXR in lipid metabolism, glucose homeostasis, and inflammation are summarized in Fig. 2.

B. LXR as cholesterol sensors

LXR act as cholesterol sensors. Cholesterol is a key cell membrane component and the essential precursor of steroid hormones, bile acids, and vitamin D. Studies from LXR-knockout mice have confirmed that LXR are important for controlling cholesterol transport, absorption, efflux, synthesis, and excretion. Increased cholesterol concentration results in the accumulation of cellular oxysterols, which activate LXR. Activation of LXR protects cells from cholesterol overload by suppressing cholesterol biosynthesis (65), stimulating reverse cholesterol transport (RCT) from peripheral tissue, activating the conversion of cholesterol to bile acids in the liver, and decreasing intestinal cholesterol absorption (70). Accordingly, accumulation of cholesteryl-esters occurs in the liver when LXRα-knockout mice are challenged with a high-cholesterol diet (71).

Although LXRα and LXRβ are highly related, LXRα appears to be the dominant isoform in the liver. Mice lacking LXRα ($LXR\alpha^{-/-}$) showed impaired hepatic function when fed diets containing cholesterol (71). $LXR\beta^{-/-}$ mice, however, maintain their resistance to dietary cholesterol (72), indicating a more prominent role for LXRα than LXRβ as a hepatic sensor of cholesterol metabolism. Bile acid signaling is a critical component in regulating cholesterol homeostasis. In rats and mice, activation of LXR prompts the conversion of cholesterol to bile acids through LXRα-mediated stimulation of cytochrome

Figure 2.

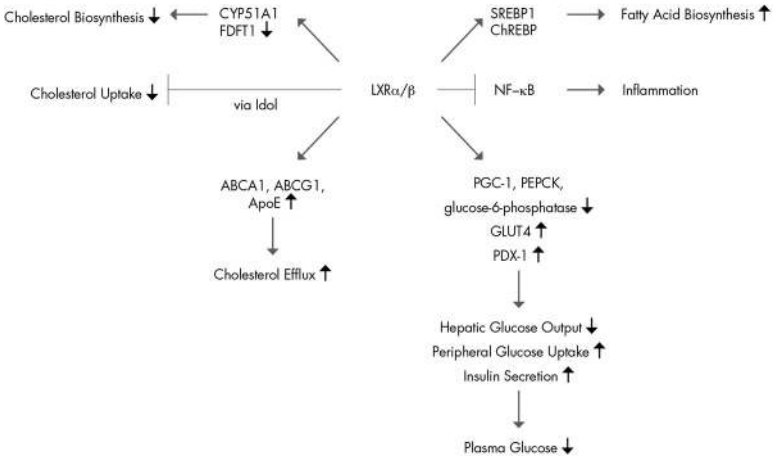

Figure 2. Roles of LXR in lipid metabolism, inflammatory response, and glucose homeostasis. Regulation of cholesterol and fatty acid metabolism by LXR in the presence of LXR ligands. In addition, activation of LXR can decrease plasma glucose levels by reducing hepatic glucose output, increasing peripheral glucose uptake in adipose tissue, and enhancing insulin secretion from pancreatic β-cells. LXR can also regulate inflammatory signaling in macrophages by inhibiting NF-κB-dependent induction of proinflammatory gene expression. Idol, Inducible degrader of the LDLR; PGC-1, PPAR-γ coactivator-1α; PEPCK, phosphoenolpyruvate carboxykinase; GLUT4, glucose transporter type 4; PDX-1, pancreatic duodenal homeobox-1.

P450 7a1 (Cyp7a1) transcription (73). Cyp7a1 is the rate-limiting enzyme in bile acid synthesis and its hepatic expression increases in response to high cholesterol levels. Mice overexpressing Cyp7a1 (Cyp7a1-tg mice) are protected against high-fat diet-induced hypercholesterolemia, obesity, and insulin resistance (74). In addition, up-regulation of Cyp7a1 stimulates hepatic bile acid synthesis and biliary cholesterol secretion without increasing intestinal cholesterol absorption in mice (75). LXRα, but not LXRβ (72), knockout mice are unable to adequately regulate the conversion of cholesterol into bile acids and thus accumulate large amounts of cholesterol esters in the liver due to the failure of inducing Cyp7a1 gene expression (71).

RCT is a process of excess cholesterol transport from peripheral tissue to the liver. In peripheral cells such as macrophages, LXR control the expression of several genes involved in RCT, including cholesterol-efflux transporters *ABCA1* and *ABCG1*, phospholipid transfer protein (*PLTP*), and apolipoproteins of the apoC subfamily and apoE (76). In diseases such as atherosclerosis, accumulation of cholesterol in macrophages is a primary event in the development of atherosclerosis (77) and the removal of excess cholesterol from macrophages by LXR reduces atherosclerosis (78). ABCA1 is a key protein that mediates secretion of cellular free cholesterol and phospholipids to lipid-poor apolipoproteins in the plasma, such as apoA-I, to form high-density lipoprotein (HDL). Besides, ABCG1 and ABCG4 also regulate cellular cholesterol efflux to HDL but not to lipid-poor apoA-I (79). HDL formation is the well-known pathway that can eliminate excess cholesterol from peripheral cells and conveys it to the liver for biliary excretion. Once HDL are taken up by the liver, LXR promote cholesterol secretion. *In vitro* experiments showed the direct interaction of LXRβ with ABCA1 and the regulation of ABCA1 by LXRβ at both transcriptional and posttranslational levels in HEK293 cells (80). Moreover, Chawla *et al.* (81) showed that LXRα is a direct target of PPARγ. PPARγ can induce macrophage ABCA1 expression and cholesterol removal from macrophages mediated by LXRα, suggesting a PPARγ-LXR-ABCA1 pathway in macrophage cholesterol efflux and atherogenesis.

Intestinal cholesterol absorption has been shown to be a major determinant of plasma cholesterol levels. ABCG5 and ABCG8 are two other ABC transporters that are thought to be involved in intestinal sterol transport and important for the secretion of cholesterol into bile. The response of ABCG5 and ABCG8 to cholesterol requires LXR. In humans and mice, LXR activation results in a reduced absorption of intestinal cholesterol mediated by ABCG5 and ABCG8 (82). The importance of ABCG5 and ABCG8 in controlling intestinal cholesterol absorption can be underscored by sistosterolemia, a genetic disease caused by mutations in these transporters that lead to abnormal hyperabsorption of cholesterol and premature coronary artery disease in patients (83).

Cellular cholesterol levels are controlled by uptake, synthesis, and efflux. LXR increase cholesterol efflux by up-regulating ABCA1 and ABCG1, as discussed above. The biosynthesis of cholesterol at the transcriptional level has been shown to be regulated by SREBP-2 and LXR. SREBP-2 up-regulates a set of genes involved in cholesterol uptake [*e.g.* low-density lipoprotein (LDL) receptor (LDLR)] and synthesis [*e.g.* 3-hydroxy-3-methylglutaryl-CoA reductase (*HMGR*)] (84, 85). In contrast, LXRα decreases cholesterol synthesis by directly silencing the expression of two key cholesterologenic enzymes CYP51A1 and FDFT1, as demonstrated in HepG2 cells (65). It is generally agreed that SREBP-2 promotes cholesterol synthesis, whereas LXR attenuate cholesterol synthesis. In hamsters, LXR activation does not change SREBP-2 or its downstream genes (67). In contrast, activation of LXR up-regulates SREBP-2 and its regulatory genes, such as

LDLR and *HMGR* in cultured astrocytes (86) and chicken primary hepatocytes (87). It is thus possible that the LXR-regulated cholesterol synthesis is cell-type and/or species specific. In addition to regulating cholesterol efflux and synthesis, LXR decrease cholesterol uptake through transcriptional induction of inducible degrader of the LDLR (*Idol*) by promoting the degradation of LDLR (47) (Fig. 2), which constitutes a complementary pathway to SREBP-2-regulated cholesterol uptake.

Collectively, LXR help maintain cholesterol homeostasis through promotion of efflux, down-regulation of synthesis and absorption, and suppression of uptake and thus prevent cholesterol accumulation.

C. LXR and apoE

ApoE belongs to the soluble apoprotein gene family. Soluble apoproteins bind to the polar heads of phospholipids at the water-lipid interface of micelles. ApoE is a surface constituent of plasma lipoproteins that plays a key role in maintaining plasma cholesterol homeostasis by facilitating efficient hepatic uptake of lipoprotein remnants from the periphery (88, 89). ApoE is expressed in various organs such as liver, brain, adrenal glands, spleen, and kidney (90). The abundance of apoE mRNA is highest in the liver, followed by the brain.

The human apoE protein is a polymorphic 299-amino-acid glycoprotein with variable levels of posttranslational sialylation (91). It is synthesized in the endoplasmic reticulum followed by transport to the Golgi and trans-Golgi network and then incorporated into vascular structures before being exported to the plasma membrane and secreted (92). ApoE has two independently folded domains, a 22-kDa N-terminal domain (residues 1–191) where apoE interacts with members of the LDL receptor family and a 10-kDa C-terminal domain that contains the major lipoprotein-binding elements (93, 94). The high-resolution structure of the N-terminal domain of apoE was identified about 20 yr ago (95). The conformational information of the C-terminal domain of apoE (residues 201–299), however, was obtained recently by the employment of pyrene fluorophores (94). It was reported that the C-terminal domain is necessary for the assembly of infectious hepatitis C virus (96). In humans, the polymorphism of the apoE gene results in three alleles ($\varepsilon 2$, $\varepsilon 3$, and $\varepsilon 4$) from the same gene residing at a single gene locus on chromosome 19 (97, 98) and leads to six different genotypes: E2/2, E2/3, E2/4, E3/3, E3/4, and E4/4. The $\varepsilon 3$ allele accounts for the highest fraction of the apoE gene pool (70–80%). In contrast, the $\varepsilon 2$ and $\varepsilon 4$ alleles account for only 5–10 and 10–15%, respectively. The three isoforms differ only at two amino acid positions 112 and 158: E2 (Cys^{112}, Cys^{158}), E3 (Cys^{112}), Arg^{158}), and E4 (Arg^{112}, Arg^{158}). Nonetheless, these single amino acid alterations at positions 112 and 158 result in profound functional differences between the three apoE isoforms (99). The structural and biophysical properties of apoE4 distinguish it from other isoforms by domain interaction, reduced stability of the N-terminal domain, and lack of cysteine, which are potentially associated with astrocyte dysfunction and impaired maintenance of neurons (93, 99, 100). The presence of an $\varepsilon 4$ allele for the apoE gene is considered the main genetic risk factor for SAD. Individuals with one or two copies of apoE $\varepsilon 4$ alleles have a younger age at onset and a greater risk for developing AD compared with carriers of other isoforms (101). In contrast, apoE2 is associated with the lowest risk and highest age of onset, whereas apoE3 is associated with the intermediate risk and age of onset.

ApoE acts as a ligand for LDLR. A primary function of this protein is to regulate the removal of receptor-mediated lipoprotein particles from the blood by endocytosis. After endocytosis of apoE-containing lipoprotein particles, mediated by an LDLR family member, apoE can be either degraded or recycled back to the cell surface for intracellular lipid trafficking (89). ApoE regulates hepatic uptake of chylomicron remnants, very-low-density lipoproteins, and some subpopulation of HDL and thus plays an important role in the transport of cholesterol and other lipids to various cells of the body. The critical role for apoE in lipid metabolism, especially in regulating plasma cholesterol homeostasis, has been highlighted by the massive accumulation of cholesterol observed in the plasma of apoE-deficient mice (102–104). ApoE-deficient mice have a more than 8-fold elevation of plasma cholesterol on a low-fat, low-cholesterol chow diet. When challenged with a high-fat diet, these animals have 13-fold higher plasma cholesterol levels than control mice.

ApoE is synthesized primarily in the liver. Liver generates about 70% of the total body apoE (105, 106). ApoE is also secreted by other cell types including macrophages and adipocytes (92, 107, 108). In addition to a proximal promoter element, two distal enhancers, termed multienhancer 1 (ME.1) and multienhancer 2 (ME.2), have been identified in the human apoE gene, which direct macrophage- and adipose-specific expression in transgenic mice (109). The expression of apoE is influenced by many different processes including development and differentiation (110, 111). Cytokines such as granulocyte-macrophage colony-stimulating factor and TGF-β can regulate macrophage apoE expression (112, 113), with down-regulation of apoE secretion by granulocyte-macrophage colony-stimulating factor and up-regulation of apoE expression by TGF-β. In macrophages, apoE transcription is directly regulated by certain transcription factors including activator protein-1

(113, 114), NF-κB (114), PPARγ (115), and LXR (116, 117). In adipose tissues and adipocytes, apoE expression is regulated by PPARγ and the proinflammatory cytokine TNF-α. TNF-α reduces apoE expression in adipocytes, an effect mediated by the binding of NF-κB in the apoE promoter (118). PPARγ agonists increase adipocyte and adipose tissue apoE expression *in vitro* and *in vivo* (119). Adipocyte apoE expression leads to increased adipocyte triglyceride (TG) content, and thus, apoE-knockout ($apoE^{-/-}$) mice have less body fat and smaller adipocytes compared with wild-type controls (120). In apoE-knockout adipocytes, PPARγ-induced TG accumulation is suppressed or abolished, indicating the function of apoE in adipocyte TG metabolism (120). The stimulation of adipocyte apoE expression by PPARγ agonist is completely eliminated by knockdown of LXR expression, suggesting a PPARγ-LXR-apoE cascade in adipocytes (121).

Different from its function in adipocytes, macrophage-specific expression of apoE is critical for the removal of excess cholesterol from macrophages and plays an important role in the prevention of atherosclerotic development (122). In macrophages, apoE is a direct target of LXR. LXR can regulate apoE transcription by interaction with a conserved LXRE present in both ME.1 and ME.2 regions of the apoE gene in macrophages and adipocytes (116). Activation of LXR by a synthetic LXR agonist, T0901317, results in the rapid and robust increase in the levels of lipidated forms of apoE (123). In contrast, the ability of natural or synthetic LXR ligands to regulate apoE expression in adipocytes and peripheral macrophages is reduced in $LXR\alpha^{-/-}$ or $LXR\beta^{-/-}$ mice and abolished in LXRα/β double-knockout animals. The basal apoE level is not compromised in LXR-deficient mice, indicating that LXR mediate lipid-induced rather than the tissue-specific expression of the apoE gene. ApoE expression by LXR in macrophages is essential for cholesterol efflux and the prevention of atherosclerotic development. The signaling pathways involved have been shown to be c-Jun N-terminal kinase and phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB, also known as Akt/related to protein kinase A and C) (117).

D. LXR in lipogenesis and glucose homeostasis

In addition to their functions in cholesterol homeostasis, LXR also play a key role in lipogenesis and glucose homeostasis. Lipogenesis is a process that leads to the *de novo* synthesis of FA. This metabolic pathway provides cells with the FA required for major cellular processes that are primarily associated with TG for FA storage (124). In mammals, liver is the major site for lipogenesis. LXR can regulate hepatic cholesterol, FA, and TG metabolism through SREBP. SREBP are transcription factors that are synthesized and located within the smooth endoplasmic reticulum membrane in their precursor form (125). There are three SREBP isoforms in mammals designated SREBP-1a, SREBP-1c, and SREBP-2. SREBP-1c and SREBP-2 are predominantly expressed by the liver (126). In contrast, SREBP-1a has a more potent transcriptional activity and is widely expressed by most tissues. SREBP-1a and SREBP-1c are splice variants encoded by the same gene (127). Results to date support the notion that SREBP-1 is a potent activator involved in the biosynthesis and esterification of FA (128, 129), whereas SREBP-2 is the prominent isoform supporting cholesterol synthesis and uptake in the liver, as mentioned earlier (130). Both SREBP-1a and SREBP-1c are involved in hepatic lipogenesis. Transgenic mice expressing truncated SREBP-1a show massive liver enlargement due to the overproduction of cholesterol and FA (131). Expression of a dominant-positive truncated form of SREBP-1c in mice also leads to a moderate increase in TG, but not cholesterol, in the liver (132). Shimano *et al.* (132) also demonstrated that several cholesterol biosynthetic enzymes were elevated in SREBP-la- but not in SREBP-1c-transgenic mice, suggesting that SREBP-la exerts stronger effects on lipogenesis than SREBP-1c. However, SREBP-la is expressed only at low levels in the liver of adult mice, rats, and humans (132). The expression of SREBP-1c is 10 times more abundant than SREBP-1a in the liver (128, 133), indicating that SREBP-1c is the main isoform involved *in vivo* in the control of lipogenesis in adults. LXR directly activate SREBP-1c transcription through two LXRE-binding sites present in the SREBP-1c promoter. The expression of SREBP-1c is abolished in LXRα/β-null mice. Conversely, activation of LXR stimulates lipogenesis in hepatocytes mainly via SREBP-1c, which leads to liver steatosis and hypertriglyceridemia (70, 134). In addition, LXR up-regulate the expression of several downstream target genes of SREBP-1c, including lipoprotein lipase (*LPL*) (135), acetyl-CoA carboxylase (*ACC*) (136), *FAS* (137), and stearoyl-CoA desaturase-1 (*SCD-1*) (138, 139).

Treatment of SREBP-1c-deficient mice with the synthetic LXR agonist T0901317 has been reported to increase lipogenic gene expression, suggesting the existence of other mechanisms by which LXR can enhance hepatic lipogenesis independently of the SREBP-1c pathway (140). The carbohydrate response element-binding protein (ChREBP) has been identified as such a LXR target. Activation of LXR increases not only ChREBP mRNA level but also ChREBP activity, leading to the up-regulation of lipogenic genes. Together, LXR can directly regulate SREBP-1 and ChREBP, which in turn enhance hepatic FA synthesis, as summarized in Fig. 2.

Although considerable evidence suggests that LXRα is the predominant isoform in the liver in the regulation of cholesterol metabolism and lipogenesis (66, 71, 72, 141, 142), LXRβ seems to be the main LXR subtype regulating lipogenesis in skeletal muscle (143). LXR agonist T0901317 increases lipogenesis and cholesterol efflux in LXRα-knockout mice and wild-type myotubes but not in LXRβ-knockout cells, demonstrating a major role for LXRβ in lipogenesis in skeletal muscle.

In addition to their lipogenic action, LXR have been shown to play a role in the control of glucose homeostasis in the body. In 2003, Tontonoz's group (144) first demonstrated that activation of LXR improves glucose tolerance in liver and adipose tissues. In the liver, the gluconeogenic genes including PPARγ coactivator-1α (*PGC-1*), phosphoenolpyruvate carboxykinase (*PEPCK*), and glucose-6-phosphatase (*Glc-6-Pase*) were suppressed. In contrast, the expression of glucokinase was induced, which promotes hepatic glucose utilization. It was also reported that LXR agonist T0901317 suppresses hepatic glucocorticoid receptor (*GR*) gene expression, which is crucial for glucocorticoid-induced insulin resistance and hepatic gluconeogenesis linked to the development of type 2 diabetes mellitus (T2DM) (145). The latter effect may contribute, at least in part, to LXR-induced reduction of hepatic glucose production. Results from both *in vivo* and *in vitro* experiments have shown that LXR up-regulate *GLUT4*, the insulin-dependent glucose transporter, in adipose tissue and 3T3-L1 adipocytes, suggesting a role for LXR in the insulin-induced increase in peripheral glucose uptake.

In pancreatic β-cells, LXR activation increases insulin secretion and insulin mRNA level (134, 146, 147). Moreover, LXR agonists increase the protein expression of *ABCA1*, *SREBP-1*, *FAS*, acetyl-CoA carboxylase, and glucokinase. The mechanisms involved are believed to be mediated via SREBP-1c. Because the controls of lipid and glucose metabolism are tightly linked, LXR can thus modulate insulin biosynthesis and secretion via the regulation of glucose and lipid metabolism in pancreatic β-cells (146). Both LXRα and LXRβ isoforms are expressed in pancreatic islets. LXRα is highly expressed in pancreatic α-cells compared with β-cells. In contrast, LXRβ is the major isoform in pancreatic β-cells, suggesting that LXRβ is the main subtype responsible for regulating insulin production and secretion in pancreatic β-cells (146). In addition, LXR agonist T0901317 stimulates the expression of pancreatic duodenal homeobox-1 (*PDX-1*), a key regulator of insulin gene expression that is critical for maintaining the β-cell phenotype and mass (147). Pancreatic β-cells isolated from LXR$\beta^{-/-}$ mice exhibit reduced *PDX-1* and insulin expression. Therefore, LXRβ is mandatory for the maintenance of pancreatic β-cell structure and function. Variation in LXRβ impairs insulin secretion, which may facilitate the development of T2DM (148).

LXR activation possesses antidiabetic properties. LXR activation normalizes glycemia and improves insulin sensitivity in rodent models of T2DM, mainly through the suppression of hepatic gluconeogenesis (70). Administration of synthetic LXR agonist T0901317 normalizes plasma glucose levels in db/db mice and Zucker diabetic fatty rats, two rodent models of T2DM and insulin resistance. Of note, LXR activators do not affect glycemia in nondiabetic animals. Conversely, glucose can activate LXR at physiological concentrations expected in the liver as demonstrated in HepG2 cells (149). The expression of LXR target genes involved in cholesterol homeostasis, for example, ABCA1, ABCG1, and ABCG5, is also significantly induced. It should be noted that glucose-mediated activation of its target genes in the liver might also occur by a LXR-independent mechanism (150).

Taken together, activation of LXR can decrease plasma glucose levels likely by reducing hepatic glucose output, increasing peripheral glucose uptake in adipose tissue, and enhancing insulin secretion by pancreatic β-cells (Fig. 2).

III. Lipid Metabolism and Its Regulation by LXR in the Brain

A. Cholesterol in the brain

The brain is the most cholesterol-rich organ in the body. In humans, the brain accounts for less than 10% of total body mass, yet it contains about 25% of total body cholesterol. Cholesterol is highly required by both neurons and glial cells in the brain for both cell function and membrane structures like axons, dendrites, and synapses. Because the CNS is segregated from the peripheral circulation by the blood-brain barrier (BBB), the source of cholesterol in the CNS has long been a debated issue. Cholesterol is transported in the circulation via lipoproteins. Although Brankatschk and Eaton (151) has recently reported that lipoprotein particles cross the BBB in *Drosophila*, it is generally agreed that plasma lipoproteins are not able to cross the BBB, at least in rats, mice, sheep, and humans (152–156). Compelling evidence using tritiated water ([^{3}H]water) in rats unambiguously demonstrated the *in situ* cholesterol synthesis in the brain (154). Peripheral radioactive cholesterol does not enter the CNS. Brain cholesterol is thus locally synthesized *de novo* by cells within the CNS. In the adult CNS, about 70–80% of total cholesterol is present as myelin, of which it is a major constituent. Brain cholesterol is synthesized predominantly by glial cells, the most abundant cell type in the

brain (152, 154). Although neurons have a high demand for cholesterol for their development and maintenance of their membrane-rich structure, they do not efficiently synthesize cholesterol and thus depend on an external source of this lipid from glial cells (155, 157, 158). Cholesterol derived from glia promotes synaptogenesis and stimulates the axonal growth of CNS neurons (159, 160). In the CNS, cholesterol synthesis is necessary for early brain development and peaks during myelinogenesis. Its synthesis continues but is decreased with age and mainly occurs in astrocytes, whereas absolute cholesterol content remains at a stable level (161, 162).

In peripheral tissues, cholesterol homeostasis is achieved by a lipoprotein shuttle between the liver and other organs through blood circulation. Because the CNS is cut off from the periphery by the BBB, cholesterol metabolism in the CNS differs greatly, and their cholesterol content must be regulated differently to reach a stable level. The active system for redistribution and recycling of cholesterol in the brain is also physically distinct from that found for plasma cholesterol.

Cholesterol is transported between cells in the form of apoE-containing lipoprotein particles. In astrocytes, cholesterol is associated with apoE-containing lipoproteins and then secreted. It is still unknown how lipoproteins are assembled and secreted by astrocytes. ApoE is the main apolipoprotein present in the CNS and the carrier predominantly secreted by astrocytes that is required for normal secretion of astrocyte lipoproteins. The key role for apoE in cholesterol metabolism is emphasized by the suppression of lipoprotein secretion found in apoE$^{-/-}$ astrocytes (163). Astrocytes from apoE$^{-/-}$ mice secrete little, if any, phospholipids or free cholesterol, indicating an important effect of apoE expression on the assembly of astrocyte lipoproteins.

Nascent cholesterol-containing lipoprotein particles released from astrocytes are first lipidated before being exported to neighboring neurons. The lipidation of nascent particles is a process mediated by specific subtypes of the ABC transporters, namely ABCA1, ABCG1, and ABCG4 (164–166). ABCA1 is expressed by both neurons and glia (167). In the CNS, glial ABCA1 plays a key role in facilitating cholesterol efflux to apoE. It mediates cellular cholesterol efflux from the inner to the outer layer of the cell membrane, thus enabling the binding of cholesterol to apolipoproteins. ABCA1-deficient primary astrocytes and microglia are impaired in their ability to efflux lipids to apoE (168). In addition, apoE secretion from ABCA1$^{-/-}$ glial cells is compromised *in vitro* due to the lack of ABCA1 expression. Mice deficient in ABCA1 have the reduced cholesterol content and the diminished size of apoE-containing cerebrospinal fluid lipoproteins (168, 169). These results suggest that ABCA1 is required for normal CNS apoE levels and for lipidation of astrocyte-secreted apoE. ABCG1 and ABCG4 are two other ABC transporters. Their primary function is to control intracellular cholesterol movement and homeostasis (170). ABCG1 and ABCG4 are highly expressed in the brain and are found in both astrocytes and neurons (171). Tarr and Edwards (172) proposed that ABCG1 and ABCG4 mediate the intracellular cholesterol transport within both neurons and astrocytes to regulate cholesterol homeostasis in the brain through SREBP-2. Deficiency of these two ABC transporters leads to defective efflux and accumulation of cholesterol and desmosterol, a known LXR activator, in primary astrocytes. Therefore, these three transporters work synergistically, leading to the exhaustive removal of cholesterol from cells.

The neuronal uptake of lipoproteins is mediated by specific receptors. Among the different family members, two receptors are most likely involved in cholesterol transport in the brain, namely the LDLR and the LDLR-related protein 1 (LRP1). Using *in situ* hybridization and immunohistochemistry, LDLR is shown to be expressed in both neurons and glial cells (173, 174), whereas LRP1 is predominantly expressed by neurons only (175, 176). LDLR and LRP1 mediate the uptake of cholesterol- and apoE-containing lipoproteins in CNS neurons, and neuronal cholesterol uptake helps to maintain synaptic integrity. Overexpression of LDLR in the brain has been shown to markedly inhibit Aβ deposition and increase Aβ clearance in LDLR-transgenic mice (177). The intracellular redistribution of lipoprotein-derived cholesterol in neurons is mediated by two components of late endosomes/lysosomes, namely Niemann-Pick type C1 (NPC1) and C2 (NPC2). NPC1 is a transmembrane protein involved in the retroendocytic shuttling of substrates to the Golgi and possibly elsewhere in cells as part of an essential recycling/homeostatic control mechanism (178–180). NPC2 is a soluble lysosomal protein known to bind cholesterol (181). Mice deficient in NPC1 or NPC2 have a devastating cholesterol-glycosphingolipidosis of the brain and show marked defects in the CNS including the development of axonal degeneration and progressive loss of specific neuronal cell types and glial cells (182–185). The process of cholesterol transport from astrocytes to neurons is summarized in Fig. 3.

B. Regulation of cholesterol homeostasis in the brain by LXR

Despite its essential role in the brain, a cholesterol overload is detrimental. Imbalances in the metabolism of lipids, especially cholesterol, are closely linked to several CNS diseases such as AD (186, 187), NPC disease (188),

Figure 3.

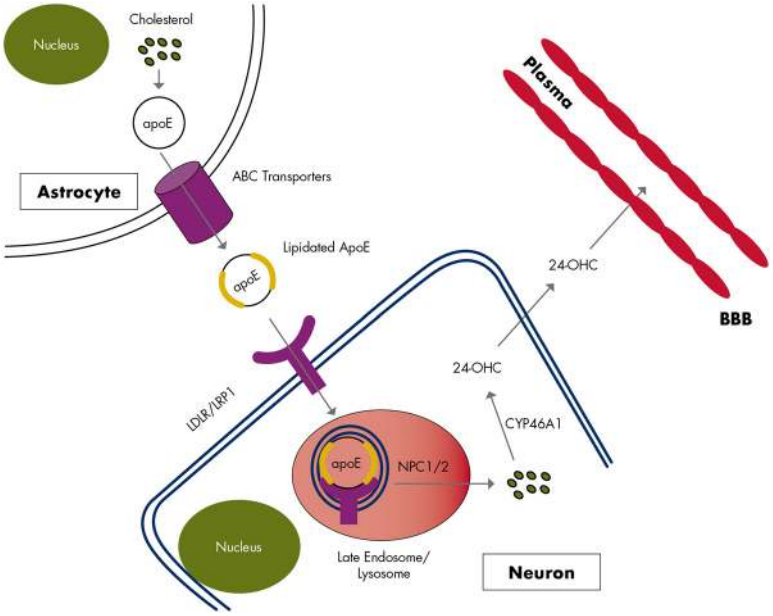

Figure 3. Schema of cholesterol metabolism in the brain. Cholesterol is mainly produced by astrocytes in the brain. In the astrocytes, cholesterol is associated with apoE-containing lipoproteins and then secreted. Cholesterol-containing lipoprotein particles (apoE-LP) released from astrocytes are lipidated and transported by transporters ABCA1, ABCG1, and ABCG4 before being taken up by neighboring neurons. Uptake of lipoprotein particles by neurons is likely through LDLR and LRP1 receptors. Thereafter, apoE-LP is redistributed within neurons, a process mediated by NPC1 and NPC2. Excess cholesterol is converted into 24OHC in neurons primarily through 24-hydroxylase (CYP46A1) and then excreted from the brain.

and Smith-Lemli-Opitz syndrome (189, 190). It is still uncertain whether both neurons and glia need to deal with cholesterol overload. Pfrieger and Ungerer (162) proposed the handling of surplus cholesterol through three possible manners by neurons, namely esterification after storage and stored within neurons as cholesterol esters, secretion via ABC transporters, and elimination by oxidization. In the first manner, excess cholesterol is presumed to be stored within lipid droplets in cells (191). However, it still needs to be confirmed whether cholesterol can be stored in its esterified form in neurons or astrocytes. In the second manner, ABCA1, ABCG1, and ABCG4 are shown to be predominantly expressed by neurons and at low levels by glial cells (170, 172, 192). It is therefore likely that neurons dispose cholesterol directly via ABC transporters (193). Astrocyes might act in a different way because they produce cholesterol in excess for its release to neurons. The third manner by which excess cholesterol is eliminated from the CNS is now widely accepted. Based on this concept, when cholesterol synthesis exceeds the needs in the adult brain, it must be eliminated by oxidization, which generates oxysterols. Three abundant naturally occurring oxysterols are 24(S)-hydroxycholesterol (24OHC), 25-hydroxycholesterol (25OHC), and 27-hydroxycholesterol (27OHC), which are termed oxysterols (194). The oxidized cholesterol products oxysterols are the ligands for LXR, as mentioned earlier. This oxidization process is mediated by cholesterol 24-hydroxylase (CYP46A1), cholesterol 25-hydroxylase (CH25H), and cholesterol 27-hydroxylase (CYP27A1), respectively. CYP46A1 is of particular interest because it is largely brain specific, whereas the other cholesterol oxidases CYP27A1 and CH25H are expressed more broadly.

24OHC is almost exclusively formed in the brain and is a secreted product of cholesterol metabolism in the CNS. The conversion of cholesterol into 24OHC is primarily mediated through the action of CYP46A1, an oxidative enzyme that belongs to the cytochrome P450 family and is mainly localized to neurons (195, 196). In contrast to cholesterol, 24OHC can cross the BBB and enter the circulation. It has been shown that 24OHC present in the circulation originates from the brain and plasma 24OHC levels markedly depend on age (197). Interestingly, the release of 24OHC from neurons via LXR regulates apoE transcription (198), indicating that export of cholesterol from glia to neurons is essentially a feedback-regulated mechanism, with the orchestrated participation of LXR, ABCA1, CYP46A1, and 24OHC (199). Notably, in a recent study that shows the beneficial effect of CYP46A1 overexpression in AD, there was no obvious change in LXR target genes after the increase in 24OHC concentration (200). One possibility is that a 2-fold increase in the brain 24OHC is not high enough to activate the LXR pathway *in vivo*. Impaired cholesterol turnover caused by CYP46A1 deficiency was shown to affect brain functions, such as long-term potentiation and learning (201). Because the brain is the major source of circulating 24OHC, plasma 24OHC levels reflect the number of metabolically active neurons in the brain and, thus, the volume of gray matter structure. Indeed, in neurodegenerative diseases such as AD and multiple sclerosis, plasma 24OHC was found to be reduced proportionally with the degree of brain atrophy (198).

In contrast to 24OHC, 27OHC is formed to a lower extent in the brain than in most other organs. 27OHC can pass through the BBB, and under normal conditions, 27OHC in the CNS is thought to be imported from the circulation (202). The conversion of cholesterol into 27OHC is mediated through the action of CYP27A1. CYP27A1 is the first isolated cholesterol hydroxylase that is much more abundant than CYP46A1 and CH25H in the body (194). The brain, how-

ever, contains only trace activities of CYP27A1 (187). Similar to CYP46A1, CYP27A1 is also involved in cerebral cholesterol metabolism. There is a significant increase in brain cholesterol accumulation in CYP27A1-deficient mice, especially in females (203). In humans, the lack of CYP27A1 leads to a rare familial lipid storage disease, cerebrotendinous xanthomatosis, which is characterized by cholesterol-containing xanthomas in brain and tendons (204). CYP27A1 and CYP46A1 are differentially expressed in AD brains (205). CYP27A1 expression decreases in neurons and is not apparent around amyloid plaques. In contrast, CYP46A1 shows prominent expression in astrocytes and around amyloid plaques. In astrocytes, which express preferentially LXRβ, activation of LXR significantly stimulates the expression of CYP27A1. Impairment of CYP27A1 alters critical features of the astrocytes, from the handling and delivery of cholesterol to neurons to the release of signaling molecules (206). Increased 27OHC and decreased 24OHC are observed in the brains from deceased AD patients (207). However, CYP46A1 and CYP27A1 levels were not significantly different between AD patients and controls.

Unlike CYP27A1 and CYP46A1 that are members of the cytochrome P450 family, CH25H belongs to a smaller family of nonheme iron-containing proteins. CH25H is expressed in most tissues at low levels and plays an important role in the regulation of SREBP (208). With the examination of CH25H expression in AD brains, CH25H was found to be a susceptibility gene for SAD, and CH25H polymorphisms are suggested to be associated with different rates of brain Aβ deposition (209). Together, among the three enzymes that oxidize cholesterol, CYP46A1 is probably the most important one in the CNS, and the level of CYP46A1 may affect the pathophysiology of AD.

Cholesterol turnover is critical for cerebral functions and has to be strictly regulated in the brain. LXR represent the key sensing apparatus for maintaining cholesterol homeostasis in the body (210). It is thus likely that LXR also function as sensors that finely tune cholesterol turnover in the brain. Indeed, overload of cholesterol has been proposed as the main cause of motor neuron degeneration in LXR$\beta^{-/-}$ mice (211). In the brain, both LXR isoforms are expressed, with LXRβ being the predominant one (212). Studies of LXR-knockout mice have clarified the role of LXR in controlling brain cholesterol. The absence of LXRβ in male mice leads to impaired motor coordination associated with lipid accumulation and loss of motor neurons in the spinal cord, together with axonal atrophy and astrogliosis (211). In the LXRα/LXRβ double-knockout mice (LXR$\alpha^{-/-}$LXR$\beta^{-/-}$), the brain shows features of the accumulation of lipid deposits and closure of ventricles. Morphological changes of the choroid plexus suggest the alteration of secretion and filtration in this organ. Additionally, LXR$\alpha^{-/-}$LXR$\beta^{-/-}$ mouse brains show a loss of neurons, proliferation of astrocytes, and disorganized myelin sheaths, further implying the important function of LXR in lipid homeostasis in the brain (213).

Furthermore, several proteins involved in the trafficking of cholesterol between cells in the brain are the direct targets of LXR, such as the cholesterol receptor apoE and cholesterol transporters ABCA1 and ABCG1 (57, 116, 214). Deletion of LXR leads to reduced expression of LXR target genes (213). As discussed above, apoE is the major apolipoprotein in the brain and the major component of lipoprotein particles in the CNS. In most mammals, about 20% of the total body apoE is made in the brain, primarily by astrocytes and microglia (91, 105, 106). It mediates transport of cholesterol and other lipids between neurons and glial cells in the brain. Activation of LXR leads to a dramatic increase in apoE mRNA and protein levels both *in vivo* and *in vitro* (215). Deficiency of apoE causes neurodegeneration in the CNS during aging (216), and mice deficient in apoE exhibit an impairment of learning and memory (217–219). Likewise, deficiency of ABCA1 results in a 65% decrease in apoE levels in the whole mouse brain. It has also been demonstrated that in APP23 mice (*i.e.* harboring the APP transgene), lack of ABCA1 considerably decreases soluble brain apoE level and increases amyloid deposition (220). ABCG1 is ubiquitously expressed in adult mice, whereas ABCG4 expression is limited to the CNS. Loss of both ABCG1 and ABCG4 results in accumulation of oxysterols in the retina and/or brain, altered brain LXR expression, and changes in brain cholesterol level (170).

In a mouse model of NPC disease, administration of a synthetic LXR agonist increased the expression of ABCA1 and ABCG1 and thus raised cholesterol excretion from the brain, delayed neurodegeneration, and extended the lifespan of the NPC1 mouse (214). However, it should be noted that this agonist did not alter cholesterol synthesis or the expression of genes associated with the formation of 24OHC or neurosteroids, such as *CYP46A1*, 3α-hydroxysteroid dehydrogenase (*3αHSD*), and cholesterol side-chain cleavage enzyme (*P450scc* or *CYP11A1*). Therefore, LXR appear to regulate cholesterol homeostasis in the brain via mechanisms similar to other tissues. However, there are many aspects of cholesterol metabolism that remain to be elucidated.

IV. LXR and Innate and Adaptive Immunity

A. LXR and inflammation

In addition to their well-established roles in lipid metabolism, LXR have emerged as important modulators of

the innate and acquired immune responses. The initial clue that raises the interest in unraveling the LXR-regulated cross talk between lipid metabolism and inflammation came from studies of LXR in atherosclerosis (77, 221). Expression and function of LXR in macrophages are critical for the progression of atherosclerosis. Transplantation studies with bone marrow from wild-type or LXRα/β double-knockout mice to the irradiated mouse models of atherosclerosis provided direct evidence that LXR modulate inflammation. Deletion of LXR in transplanted bone marrow-derived cells resulted in a profound increase in atherosclerotic lesion area in mice compared with animals transplanted with wild-type bone marrow. In contrast, agonists of LXR inhibit inflammatory gene expression in the aorta of atherosclerotic mice (77, 78). LXR are known to interfere with atherosclerosis via both regulation of cholesterol transport and antiinflammatory effects (222). In the following years, accumulating evidence supported the role of LXR in both innate and adaptive immunity (45, 63, 223–230). Hong *et al.* (231) recently generated transgenic mice that exhibit increased LXR signaling selectively in adipose tissue and macrophages. Analysis of primary macrophages from these mice confirmed the up-regulated expression of genes involved in cholesterol efflux and FA synthesis. In contrast, inflammatory genes induced by lipopolysaccharide (LPS) were suppressed, supporting an important role of LXR in the coordinated regulation of lipid metabolic and inflammatory gene programs in macrophages. It has now been generally accepted that LXR function as integrators of metabolic and inflammatory signaling.

Macrophages are key innate immune cells that recognize, phagocytose, and kill invading bacteria and viruses and orchestrate inflammatory responses through the release of proinflammatory chemokines and cytokines. Macrophages also contribute to acquired immunity by antigen presentation and regulation of T-cell responses. Both LXRα and LXRβ are expressed in macrophages. Castrillo *et al.* (223) first demonstrated a cross talk between LXR and Toll-like receptor (TLR) signaling in macrophages. TLR are mainly expressed in cells of the innate immune system. Activation of TLR by ligand binding triggers proinflammatory signal transduction pathways and gene transcription. Viral and bacterial infections inhibit LXR-dependent gene expression involved in cholesterol efflux and lipid metabolism, including *ABCA1*, *apoE*, *ABCG1*, *SREBP-1*, and *FAS* in cultured macrophages (223). Activation of TLR3, which recognizes double-stranded RNA, and TLR4, the LPS receptor, severely inhibits the transcriptional activity of LXR via the transcription factor interferon-regulatory factor 3, but not NF-κB. The inhibitory effect on LXR thus leads to restrained cholesterol efflux from macrophages. Interestingly, activation of LXR antagonizes inflammatory gene expression downstream of TLR4 signaling, but not TLR3, indicating that transcription by LXR is context specific. Together, these studies outlined above suggest the ability of LXR to mediate both lipid metabolism and inflammation, which can be regulated by a feedback loop formed by LXR-TLR cross talk (232).

The role of LXR in inflammation is further supported by a series of studies performed later. *In vitro* activation of LXR inhibits the expression of inflammatory mediators such as inducible nitric oxide synthase (also known as nitric oxide synthase 2), cyclooxygenase-2, IL-6, IL-1β, and monocyte chemotactic protein-1 in response to bacterial infection or LPS, in part via blockade of NF-κB (63, 228). The negative regulation of inflammatory gene expression by LXR is mediated via transcriptional inhibition of promoters, a phenomenon referred to as transrepression, as mentioned earlier (63). Christopher Glass's (233) group has made considerable contribution to unraveling the underlying mechanisms of nuclear receptor-mediated transrepression in macrophages. They proposed that LXR regulate gene-specific transrepression via a SUMOylation-dependent pathway, which is independent of PPARγ (62). PPARγ is the first nuclear receptor family member that was shown to mediate transrepression of inflammatory response genes in a SUMOylation-dependent pathway (233). It was reported that PPARγ links to LXR in regulating cholesterol efflux (81) and adipocyte TG balance (121). Glass *et al.* (62) demonstrated that ligand binding to LXR results in SUMOylation modified by SUMO2/3, and this step is dependent on histone deacetylase-4 E3 ligase, which is different from PPARγ as PPARγ SUMOylation is modified by SUMO1 dependent on protein inhibitor of activated STAT1. Moreover, SUMO1-PPARγ and SUMO2/3-LXR inhibits distinct corepressor N-CoR clearance, allowing promoter- and TLR-specific patterns of repression. As a consequence, PPARγ and LXR can transrepress overlapping, but distinct sets of inflammatory genes. For instance, the IL-1β gene is sensitive to LXR repression only when induced by LPS in primary macrophages. In contrast, TNF-α is PPARγ sensitive. These data suggest that LXR and PPARγ regulate inflammation in different ways.

The antiinflammatory actions of LXR have now also been reported in other animal disease models, such as irritant and allergic contact models of dermatitis (224) and experimental stroke (234). Both LXRα and LXRβ are required for the potent antiinflammatory activity in irritant and allergic contact models of dermatitis by a receptor-mediated process.

B. LXR and innate and adaptive immunity

Because macrophages play a central role in innate immunity, the regulation of macrophage proliferation, survival, and functions are therefore critical to immune responses. Mice lacking LXR are highly susceptible to infection when challenged with *Listeria monocytogenes* (225), and the protective effect of transplanting bone marrow from LXR$\alpha^{-/-}$LXR$\beta^{-/-}$ mice into wild-type mice points toward macrophages as being responsible for such an increased susceptibility. LXR-deficient macrophages exhibit accelerated apoptosis and defective bacterial clearance. This phenotype results, at least in part, from the loss of regulation of antiapoptotic factor SPα (also known as apoptotic inhibitor of macrophages) by LXRα. This study demonstrates the importance of LXR-dependent gene expression for macrophage survival and for the innate immune response and suggests that the LXR signaling pathway mediates macrophage responses to modified lipoproteins and intracellular pathogens. Similar findings from Valledor *et al.* (226) also suggested that the activation of LXR/RXR heterodimers was able to prevent bacterial-induced macrophage apoptosis induced by *Bacillus anthracis*, *Escherichia coli*, and *Salmonella typhimurium*.

The presence of LXR in macrophages is also important for their phagocytic properties (230). Effective clearance of apoptotic cells by macrophages is essential for immune homeostasis, and the impairment or failure of phagocytosis results in the chronic accumulation of apoptotic remnants that might ultimately trigger autoimmunity. Apoptotic cell engulfment activates LXR and the expression of Mer, a receptor critical for phagocytosis. LXR-null macrophages exhibit a selective defect in the phagocytosis of apoptotic cells, implying an essential role for LXR in macrophage function. In addition to the effect of LXR on macrophage survival and function, a very recent study showed the inhibition of macrophage proliferation by LXR through down-regulation of cyclins D1 and B1 and cyclin-dependent kinases 2 and 4 (235).

It is interesting to note that LXR signaling is also involved in T-cell proliferation. Bensinger *et al.* (229) showed that T-cell activation is accompanied by the down-regulation of LXR target genes involved in cholesterol transport and by the simultaneous induction of the SREBP-2 pathway for cholesterol synthesis. Mice lacking LXRβ exhibit lymphoid hyperplasia and enhanced responses to antigenic challenges, indicating that LXR integrate lipid metabolism and adaptive immunity (229). Very recently, LXR were reported to regulate Th17 cell differentiation and autoimmunity via an SREBP-1-dependent pathway, which further supports a role for LXR in adaptive immunity (236).

Collectively, LXR are able to regulate differentiation, proliferation, survival, and immune functions in macrophages and T cells and thus actively participate in the innate and adaptive immunity.

V. LXR Integrate Lipid Metabolism and Neuroinflammation in AD

A. Cholesterol in AD pathology

AD is a multifactorial disease. Besides the well-known genetic causes, accumulating evidence points toward a role for lipids in the etiology of this disease (237). Dyslipidemia increases the risk of AD (238). Aberrant lipid metabolism, especially cholesterol metabolism, has been implicated in AD, and systemic cholesterol metabolism has been suggested to be related to susceptibility to AD (239, 240). The potential use of lipid-lowering agents, especially statins, to prevent or treat AD, has been extensively investigated. Data from a number of *in vitro* and *in vivo* studies and some clinical trials have suggested a beneficial effect of reducing cholesterol levels in AD (241–243). However, human studies show variable outcomes (244). Although current clinical evidence is not strong enough to support the widespread use of statins to treat AD, a few factors are recommended when evaluating the use of statins in human studies, including different BBB permeabilities among statins, the stage in AD at which statins were administered, the drugs' pleiotropic metabolic effects, and so on (43). Consideration for investigating restricted statin therapy to selected populations of AD individuals or at specific stages is strongly recommended (245).

The idea that targeting the brain lipids might regulate Aβ production has attracted much attention (246). In normal brain, CYP46A1, which converts cholesterol to 24OHC, is expressed in neurons (196). In AD brain, however, CYP46A1 staining was decreased in neurons as compared with control brains. In contrast, marked positive staining was found in glial cells in AD but not in control brains (247). Neuronal overexpression of CYP46A1 by adeno-associated virus gene therapy before or after the formation of amyloid deposits markedly reduces Aβ pathology in mouse models of AD (200). The 24-OHC content increases 2-fold in the dissected cerebral cortex and hippocampus of mice injected with wild-type CYP46A1 virus. Surprisingly, the concentration of total cholesterol remains unchanged in the cerebral cortex and hippocampus of mice injected with wild-type or mutant virus. In agreement with this study, ablation of acyl-CoA:cholesterolacyltransferase 1 (*ACAT1*), the major functional enzyme that converts free cholesterol to cholesteryl esters, increases 24OHC level in the brain and ameliorates amyloid pathology in mice with AD (248). Conversely, Hal-

ford and Russell (249) found that loss of one or both CYP46A1 alleles increased longevity in AD mice. However, the amyloid formation is not greatly affected. One opening question with this study is whether the 24OHC content in the brain of the crossed mice decreased. Although previous findings have shown an approximately 50% decrease in *de novo* cholesterol synthesis and a corresponding 50% decrease in cholesterol excretion from the brain of mice lacking CYP46A1 (250, 251), the 24OHC level in the brain of AD mice in the context of CYP46A1 gene deficiency would still be helpful to explain the amyloid formation in the crossed mice.

It has been reported that the cellular cholesterol load regulates APP processing to Aβ, with the induction of increased Aβ formation by high levels of cholesterol and, conversely, a decreased formation at low levels of cholesterol (240, 252–254). In cultured hippocampal neurons, depletion of cholesterol results in the inhibition of Aβ, suggesting that cholesterol levels have an impact on Aβ formation and that cholesterol, Aβ, and AD are interconnected (254). Recently, a study demonstrated the effect of dietary cholesterol on tau protein (255). Mice expressing the P301L mutant human tau were kept on a cholesterol-enriched diet. Highly elevated dietary cholesterol levels enhanced the progression of tau pathology in these mice, and this effect was correlated with an elevation of the levels of cholesterol metabolites of CYP27A1 in the brain.

Cholesterol efflux is now recognized as an important component of AD pathology, especially for the disease onset. The efflux pump ABCA1 is a major vector of cholesterol transport. It is required for normal apoE levels in the CNS and for lipidation of astrocyte-secreted apoE. Genetic loss of ABCA1 causes reduced apoE protein level in both cortex and cerebrospinal fluid, likely by the altered metabolism of abnormally lipidated apoE-containing lipoprotein particles. The impaired ability to efflux lipids in ABCA1$^{-/-}$ glia results in lipid accumulation in both astrocytes and microglia (168, 169). Lack of ABCA1 promotes amyloid deposition in the APP23 mouse model of AD, suggesting a role for ABCA1 in the pathogenesis of parenchymal and cerebrovascular amyloid pathology (220). Conversely, overexpression of ABCA1 in the PDAPP mouse model of AD, which harbors a mutated human APP transgene and accumulates large Aβ deposits, results in increased apoE lipidation, a significantly reduced amyloid deposition, a redistribution of Aβ in the hippocampus, and an almost complete absence of thioflavine S-positive amyloid plaques (256). In addition, genetic variability of ABCA1 influences the age at onset of AD, possibly via interfering with the homeostasis of CNS cholesterol (257). Taken together, the accumulated evidence clearly suggests that increasing ABCA1 function may likely have a therapeutic effect toward AD. Besides ABCA1, ABCG4 was found to be highly expressed in microglial cells, which were closely located to senile plaques in AD brain (258). No positive staining was observed in neurologically normal tissues.

As mentioned above, apoE is highly expressed in the brain and plays a major role in brain cholesterol transport. In the CNS, apoE is synthesized locally by nonneuronal cells, mainly astrocytes and, under normal conditions, microglia to a certain extent. By immunochemistry, apoE is shown to be localized to the senile plaques, vascular amyloid, and neurofibrillary tangles of AD (259). The role of cholesterol and apoE has been abundantly documented in the formation of amyloid plaques in AD (38, 187). There has been long and intense debate regarding the protective or detrimental roles for apoE in Aβ amyloidosis and whether apoE levels should be increased or decreased for the treatment of AD. On one side, a number of studies have shown the beneficial role of increasing apoE expression. For example, apoE-deficient mice have cognitive defects and hyperphosphorylated tau, as discussed earlier (217). A dose-dependent protective effect of apoE ε3 allele against Aβ deposition was found in the PDAPP transgenic mouse model of AD, suggesting that increasing human apoE levels in the brain might be a possible therapeutic approach for preventing AD (260). ApoE deficiency also promotes significant increases in phosphorylation and conformational changes of tau protein in P301L mice on a control diet (255). Astrocytes and microglia, which are found to surround amyloid plaques, both promote or mediate Aβ clearance via an apoE-dependent mechanism (261, 262), suggesting a protective function of apoE in Aβ clearance. In addition, administration of LXR synthetic agonist GW3965 to a transgenic mouse model of AD results in the enhanced expression of lipidated apoE, followed by a dramatic reduction of the Aβ load in the brain. These data emphasize the ability of apoE to promote Aβ degradation, which likely depends upon the apoE isoforms and their lipidation status (263). On the other side, a different opinion holds that increasing apoE degradation or inhibiting its synthesis might be an effective treatment of AD. A series of studies clearly indicated the protective effect of apoE deficiency against Aβ deposition in the PDAPP (264) or APP^{V717F} transgenic mouse models (265, 266). In a very recent research, human apoE isoform haploinsufficient mouse models were generated by crossing APPPS1–21 mice with apoE isoform knock-in mice to address how modulation of human apoE levels changes AD pathology (267). By evaluating the effect of different human apoE gene dosage on amyloid pathology, researchers found that decreasing human apoE levels, regardless of isoform status, results in significantly decreased amyloid

plaque deposition and microglial activation. At present, it is somehow difficult to reconcile these results with the findings from apoE$^{-/-}$ (217) and ABCA1 studies (220, 268) and the seeming positive role for apoE in Aβ clearance by astrocytes and microglia. There are several possible explanations for this obvious discrepancy. One possibility is that the apoE protein level in the brain is not *per se* a determinant of the amount of Aβ deposition. Rather, the specific apoE isoform that is expressed as well as its lipidation status should determine its actual functionality in the brain. Another point that should be taken into consideration is the regulation of tight junction integrity in BBB by apoE (269). BBB permeability is increased in the apoE ε4-knock-in mice and apoE-knockout mice compared with the apoE ε3-knock-in mice. We may then question the real roles for apoE in AD pathogenesis. Does apoE ε4 contribute to AD by disturbing cholesterol traffic in the brain or impairing BBB? What is the direct relationship between cholesterol efflux from the brain through the impaired BBB and the potential harmful effects of cholesterol overload in the CNS?

B. Diabetes mellitus as a risk factor for AD

Lipid metabolism is always tightly linked to glucose homeostasis. Moreover, both dementia and diabetes are frequent disorders in elderly people. Epidemiological studies have strongly suggested an increased risk for AD with diabetes mellitus (270–276). In a Rotterdam study, a total of 3139 participants were monitored for possible correlations of fasting glucose, insulin levels, and insulin resistance with the risk of AD (276). Results from the study showed that levels of insulin and insulin resistance are linked with a higher risk of AD. Similarly, the association between glucose tolerance status and the development of dementia was investigated in another long-term follow-up study (275). Their findings further support that diabetes represents a significant risk factor for all-cause AD.

How diabetes mellitus affects AD has long been a debated issue. It is now widely recognized that AD is closely associated with impaired insulin signaling and glucose metabolism in the brain. In the CNS, insulin regulates key processes such as neuronal survival and longevity, influences release and reuptake of neurotransmitters, and improves learning and memory. Insulin receptors and insulin signaling proteins are widely distributed throughout the CNS (277, 278). There are two possible sources of insulin in the brain, namely 1) the transport of insulin from the blood to the brain (279) and 2) the local production of insulin by brain insulin-producing cells or neurons (280–282). Two different types of insulin receptors have been found in adult mammalian brain. A neuron-specific brain type of insulin receptor was detected as highly expressed in neurons (283). By binding to its receptors, insulin activates PI3K and Akt/related to protein kinase A and C, and the latter inhibits GSK-3 (284), which regulates Aβ production (285). GSK-3 also phosphorylates tau protein, the principal component of neurofibrillary tangles (286). Insulin and its signaling transduction can thus control Aβ extracellular levels and the balance in tau protein phosphorylation (287). Defective insulin signaling renders neurons energy-deficient and impairs synaptic plasticity (288). Damage to the insulin signaling cascade is involved in the pathogenesis of AD. Reduced brain insulin signaling has been observed in patients with AD (289). Accordingly, intranasal insulin administration improves cognition and modulates Aβ in early-onset AD, suggesting a novel approach to the treatment of AD (290). Very recently, results from a pilot clinical trial support the intranasal insulin therapy for AD (291).

Insulin resistance is a central feature of diabetes. Aging and peripheral insulin resistance induce brain insulin resistance (292). In the context of diabetes mellitus, hyperinsulinemia or insulin deficiency lead to an imbalance of insulin-regulated tau kinases and phosphatases and thus alter tau phosphorylation. A recent study with human brain samples confirmed that hyperinsulinemia and hyperglycemia caused by insulin resistance accelerate plaque formation in combination with the effects of the apoE ε4 allele (293). In an Aβ-infusion AD rat model, induction of insulin resistance exacerbated synaptic protein loss (294). Insulin resistance appears to increase Aβ production (295). The mechanism underlying the link between AD and insulin resistance likely involves the Akt/GSK-3 (295) and wingless (Wnt) signaling pathways (296). Diet-induced insulin resistance increases GSK-3 (GSK-3α and GSK-3β) activity through attenuation of PI3k/Akt in the brain (295). Akt/PKB has the known inhibitory role on GSK-3, and GSK-3α has been previously shown to promote Aβ peptide generation by modulating the cleavage of APP at the γ-secretase site (285). The increased GSK-3α activity through attenuation of GSK-3 phosphorylation resulting from insulin resistance thus leads to increased Aβ production (295). In addition, GSK-3β has been identified as one of the major candidates mediating tau hyperphosphorylation (297). The increased GSK-3β activity can thus lead to hyperphosphorylation of tau. Insulin resistance, together with oxidative stress, an important determinant in the pathogenesis of AD, can also inhibit Wnt signaling (296). Wnt proteins inactivate GSK-3β. The inhibition of Wnt, therefore, leads to the disinhibition of GSK-3, which, in turn, promotes the formation of Aβ and tau protein phosphorylation (296). The two pathways are not completely isolated. Indeed, PI3k/Akt is known for its

Figure 4.

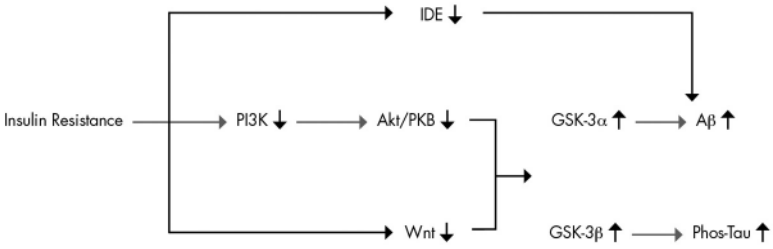

Figure 4. The mechanisms by which insulin resistance induces Aβ production and tau phosphorylation. Akt and Wnt signaling pathways are involved in the link between AD and insulin resistance. Insulin resistance attenuates PI3K/Akt(PKB) and inhibits Wnt in the brain, leading to the increased GSK-3α and GSK-3β activity. Up-regulation of GSK-3α and GSK-3β then promotes the formation of Aβ and tau protein phosphorylation (Phos-tau), respectively. In addition, insulin resistance can reduce Aβ clearance by decreasing the expression and activity of insulin-degrading enzyme (IDE), which is an enzyme involved in Aβ clearance.

role on inhibition of Forkhead box class O 1 (FoxO1) transcription activity by phosphorylation of FoxO and then promoting the nuclear exclusion of FoxO1 proteins. Insulin resistance can thus increase FoxO1 transcription activity. On the other hand, in the absence of Wnt signaling, β-catenin, a component of the Wnt signaling pathway, binds to FoxO proteins via Wnt-dependent signaling, thus up-regulating FoxO-controlled genes (296). In addition to its role in increasing Aβ production, insulin resistance can reduce Aβ clearance by decreasing the expression and activities of insulin-degrading enzyme, which is an enzyme involved in Aβ clearance (295). The mechanisms by which insulin resistance induces Aβ production and tau phosphorylation are summarized in Fig. 4. Toxic lipids produced as a result of peripheral insulin resistance have been proposed as another potential mechanism by which neurodegeneration is associated with peripheral insulin resistance (298). Toxic lipids, including ceramides, can cross the BBB and cause brain insulin resistance, oxidative stress, neuroinflammation, and cell death and thus lead to AD-type neurodegeneration.

It is also interesting to note that T2DM is associated with altered ABCA1 gene expression and function. ABCA1 expression is decreased in diabetic mouse macrophages and kidneys (299) and human blood leukocytes from patients with T2DM (300). Furthermore, the function of ABCA1 in cultured human skin fibroblasts is reduced in T2DM and with increasing blood glucose concentration, as evidenced from cholesterol efflux experiments (300). However, it remains unknown whether ABCA1 levels are reduced in the brain of diabetic subjects, which may contribute to the pathogenesis of AD and constitute an alternative mechanism underlying the link between diabetes and AD.

AD and T2DM share several common abnormalities, including impaired glucose metabolism, increased oxidative stress, insulin resistance, and amyloidogenesis (301). On one hand, as mentioned above, peripheral insulin resistance promotes Aβ formation and tau protein phosphorylation. On the other hand, the neurodegenerative process may also induce neuronal insulin resistance. AD is now suggested as a brain-specific form of diabetes and termed as type 3 diabetes (302). Treatment of diabetes mellitus might thus have a positive effect on AD (303). Clinical trials on the PPARγ agonist rosiglitazone, one of the former U.S. Food and Drug Administration-approved thiazolidinediones for treating T2DM, showed improved cognition and memory in patients with mild to moderate AD in a phase II study (20, 304, 305). Results from a recent phase III study, however, revealed no evident efficacy of rosiglitazone monotherapy in cognition or global function in the apoE4-negative or other analysis population (21). Although efficacy with rosiglitazone treatment was not demonstrated in this study, the role of glucose metabolic disorders in AD still needs attention, and agents that can modify insulin sensitivity, remain as therapeutic options worthy of further inquiry. Metformin, another widely prescribed insulin-sensitizing drug used in the treatment of T2DM, was also tested in various cell types (306). Different from insulin, metformin can up-regulate β-secretase via an AMP-activated protein kinase-dependent mechanism but does not affect Aβ degradation. However, when used in combination with insulin, metformin enhances the effect of insulin by further reducing Aβ levels. The incretin hormone glucagon-like peptide-1 facilitates insulin signaling. For instance, a novel long-lasting glucagon-like peptide-1 analog, liraglutide, was injected into APP/PS1, a mouse model of AD, to test its effect on AD. After 8 wk of treatment, there was a 40–50% reduction in Aβ plaque count and a 25% reduction in soluble amyloid oligomers. Iraglutide also prevented memory impairment, synaptic loss, and deterioration of synaptic plasticity, suggesting that the antidiabetic drug liraglutide might represent a novel treatment strategy for AD (307).

C. Inflammation in AD

Inflammation in the CNS (neuroinflammation) is a phenomenon occurring in the brain of AD patients and mouse models of the disease. AD brains exhibit signs of the activation of innate immune response, and numerous studies have proposed a role of the innate immunity and microglia in the pathogenesis of AD (308–310). Micro-

glia, a type of glial cell, are the brain's macrophages. As the immune cells of the CNS, microglia represent the first line of defense against invading pathogens and mediate the inflammatory response in the brain of AD individuals and animal models of the disease. A number of key innate immune receptors have been shown to be involved in the removal of Aβ. Indeed, CD14 is up-regulated in activated microglia (311), it interacts with Aβ42 and has a direct role in Aβ42 phagocytosis (312). On the other hand, high levels of CD14 were found in the brain of patients (312) and mouse models of AD (313), and mice deficient in CD14 exhibited reduced insoluble levels of Aβ and decreased plaque burden at 7 months of age (314). The possible mechanisms underlying the reduced plaque deposition involve the modulation of the innate immune response toward an M2 state of microglia by CD14. Microglia in an M2 state are the antiinflammatory subsets of cells, whereas microglia in an M1 state are the classically activated proinflammatory subsets of cells (315). TLR are a family of pattern-recognition receptors in the innate immune system and act to mobilize a robust immune reaction in response to pathogen (316). TLR function as dimers and often use coreceptors such as CD14 to assist in pathogen recognition. Emerging evidence indicates that TLR in the CNS play a role in the clearance of toxic proteins and neurons (317). Activation of TLR2 in microglia promotes cell uptake of $A\beta_{1-42}$ peptide (318) and has been shown to delay the cognitive decline in a mouse model of AD (319). Deficiency of TLR2 in mice accelerated spatial and contextual memory impairments, which correlated with increased levels of $A\beta_{1-42}$ in the brain. Data from *in vitro* experiments also demonstrated that activation of microglia with TLR2, TLR4, or TLR9 ligands significantly facilitates the phagocytosis of Aβ (320). Furthermore, Reed-Geaghan *et al.* (321) reported that microglia cultured from CD14-, TLR4-, or TLR2-null mice were unable to initiate the signaling cascade necessary for the induction of phagocytosis after exposure to fibrillar amyloid β-peptide (fAβ), suggesting that the response of microglia to fAβ requires the participation of TLR2, TLR4, and the coreceptor CD14. Consistent with cellular and animal data, the transcription of TLR3, TLR4, TLR5, TLR7, TLR8, TLR9, and TLR10 is severely reduced in macrophages taken from AD patients compared with control subjects (322). These data suggest that these innate immune receptors expressed in microglia/macrophages constitute a natural defense to prevent Aβ accumulation in the brain.

Activated microglia are colocalized with Aβ plaques and produce inflammatory mediators in response to TLR ligands and Aβ (308). Proinflammatory cytokines, including TNFα (323, 324), IL-1 (325), IL-6 (325), and monocyte chemotactic protein-1 (326) are increased in the brain of AD patients or mouse models. These cytokines could in turn affect the normal behavior of neurons (327). Furthermore, prostaglandins, especially prostaglandin E2, seem to be involved in the production of Aβ as well as in the pathogenesis of AD (328, 329). Inhibition of cytokine signaling ameliorates disease progression in animal models of AD. Conversely, administration of exogenous cytokines or overexpression of cyclooxygenase-2 in the brain increase plaque formation and accelerate cognitive impairment (330). Antiinflammation seems to be beneficial in AD. On the other hand, TNFα has been shown to exhibit neuroprotective activity by inducing the expression of the antiapoptotic factor Bcl-2 in neuronal cells (324). IL-1β, the cytokine that is up-regulated in microglial cells surrounding amyloid plaques, was found to significantly enhance Aβ cleavage (331). Moreover, the level of TGF-β, which has mainly an antiinflammatory action, is increased in the brain of AD patients (325). In addition to producing inflammatory cytokines, microglia have been identified as an important source of ROS. Activated microglia are able to generate ROS, as well as NO, and act directly on neurons to induce neurotoxic effects, which ultimately leads to neuronal cell death (332, 333).

The point at which neuroinflammation first occurs in the progression of the AD pathology is still unknown. Questions are then raised as to whether inflammatory responses play a beneficial or detrimental role in AD. One possibility is that the immune response in AD is a double-edged sword. The initial function of microglia seems to be protective in the CNS. However, upon excessive or sustained activation, microglia could significantly contribute to chronic neuropathologies, leading to neurotoxicity (334). It has to be noted that in the CNS of animal models after irradiation, there are two subsets of microglia, namely resident microglia and a more immunocompetent bone marrow-derived microglia. They seem to possess different phenotypes and functions. Allogeneic bone marrow transplantation has already been used to treat CNS genetic disease such as Hurler syndrome (mucopolysaccharidosis type IH) (335). In mouse models of AD, bone marrow-derived microglia have also been shown to delay or stop the progression of AD, and preventing their recruitment exacerbates the pathology (336–338). Stimulating the hematopoietic system might be a novel therapeutic approach for the treatment of AD.

In addition to inflammation triggered by Aβ plaques, excessive insulin stimulation invokes synchronous increases in Aβ levels and inflammatory agents (339). Chronic hyperinsulinemia may exacerbate inflammatory responses and increase markers of oxidative stress (288). In the context of diabetes mellitus, antidiabetic agents may be optimal treatment options for patients with AD (20).

D. LXR integrate lipid metabolism and inflammation in AD

A growing body of literature now supports the idea that lipid metabolism and inflammation are closely linked. A recent study demonstrated the elevation of microglial activation and the reduction of neuronal development induced by a high-fat/high-cholesterol diet (340). LXR appear to play a role in integrating lipid metabolism and neuroinflammation in AD. Indeed, LXR up-regulate ABCA1 and apoE, which are intimately involved in Aβ transport and clearance. Activation of these genes by LXR agonists in the brain may have a significant impact on Aβ deposition and amyloid/neuritic plaque formation (50). Deletion of either LXRα or LXRβ in APP/PS1 AD-Tg mice resulted in an increased amyloid plaque load and exacerbated AD pathology (341). This effect was attributed to the defects in brain cholesterol metabolism and to the ability of LXR to inhibit the inflammatory response of microglia in the presence of fAβ. Moreover, high-fat/high-cholesterol diets accelerate AD-like neuropathology in mouse models likely by inducing neuroinflammation and APP processing (342–344). Administration of synthetic LXR agonist T0901317 increases protein levels of ABCA1 and apoE, decreases Aβ levels in the brain, and thus ameliorates amyloid pathology and memory deficits caused by high-fat/high-cholesterol diets in APP23 mice (345). These data, together with the ability of LXR agonists to attenuate the expression of inflammatory genes in the presence of LPS, underline a possible correlation between the antiinflammatory effects of LXR and their protective effects in AD.

It still remains controversial as to whether the inflammatory response plays a beneficial or detrimental role in brain diseases, including AD (330). Indeed, data from clinical trials have shown that administration of two nonsteroidal antiinflammatory drugs failed to improve cognitive functions and was even detrimental in some patients (346). It is therefore premature to conclude that the beneficial effect of LXR agonists in AD is to be attributed to their antiinflammatory properties. Recent studies have demonstrated a protective role of bone marrow-derived microglia in AD mouse models (336, 338, 347). Very recently, Li *et al.* (348) reported a significant amelioration of atherosclerosis as well as hypertriglyceridemia by hematopoietic stem cell-based macrophage LXRα gene therapy. Although such a distinction between cell subsets has

Figure 5.

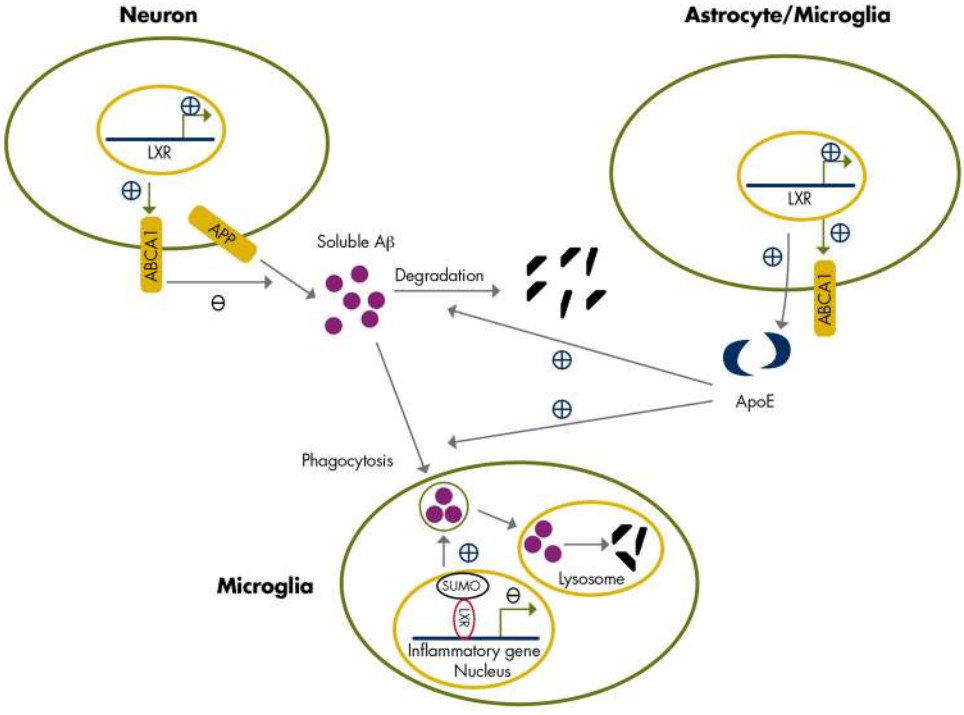

Figure 5. Effects of LXR on soluble Aβ production and degradation. The level of soluble Aβ is controlled by its production from neurons and its subsequent clearance. Activation of LXR increases the expression of ABCA1 and apoE and seems to attenuate AD pathology through the following mechanisms. 1) Activation of LXR up-regulates ABCA1 expression, which inhibits neuronal Aβ secretion. 2) LXR modulate inflammation and increase the phagocytotic capacity of microglia for Aβ. 3) LXR induce apoE transcription in astrocytes and microglia, which promotes Aβ degradation and clearance.

yet to be determined in studies investigating the link between LXR, inflammation, and AD, macrophage LXR expression by bone marrow transplantation may be of potential value for the treatment of AD. On the other hand, LXR activation might facilitate the phagocytic clearance of fAβ by a microglial cell subset and explain the increased amyloid deposition in LXR-null mice. Our understanding of the mechanisms by which LXR regulate neuroinflammation in AD is far from complete, and much work is needed to unravel the underlying mechanisms and to determine whether a direct link exists between these events.

Treatment of APP-expressing cells with LXR activators increases ABCA1 expression (257), a direct target gene of LXR, whereas ABCA1-mediated translocation of membrane cholesterol leads to decreased Aβ formation via reduced γ-secretase cleavages (349). LXR synthetic agonist T0901317 significantly decreased Aβ via up-regulation of ABCA1 expression in cultured Chinese hamster ovary cells selected for stable expression of a mutated form of human APP (CHOAPPsw cells) and primary neurons. *In vivo*, administration of T0901317 to APP23 transgenic mice increased ABCA1 expression, facilitated the clearance of Aβ42, and markedly reduced the soluble Aβ42 levels in the brain (48, 350). The long-term use of LXR agonist T0901317 increases ABCA1 and apoE expression in astrocytes, which is critical for microglial phagocytosis, and then efficiently reduces insoluble and soluble Aβ levels in APP23 mice (351). However, the authors found that although the long-term use of T0901317 efficiently reduced Aβ levels in mice, spatial learning in the Morris water maze was only slightly improved (351). Differently, Donkin *et al.* (352) showed that treatment of APP/PS1 mice, another amyloid mouse model of AD, with synthetic LXR agonist GW3965 significantly improved the mouse performance in the Morris water maze task compared with untreated APP/PS1mice. The treated APP/PS1 mice also completely restored novel object recognition memory to wild-type levels as proved in the novel object recognition experiment. The discrepancy with regard to the memory and learning after the treatment is probably due to different animal models, the elaborate functions of the two synthetic LXR agonists, and the age of mice to receive the treatment. This study also confirmed that GW3965 increases ABCA1 and apoE protein levels and that ABCA1 is required for the restoration of memory and elevated apoE level in the brain and cerebrospinal fluid upon the treatment with GW3965. In summary, LXR activation is able to increase cholesterol efflux from glial cells and reduce Aβ secretion from neurons via an ABCA1-mediated process (212).

Activation of LXR has beneficial effects on glucose control in mouse models of T2DM (353). Additionally, a recent study showed the protective effects of LXR activation on diabetes-induced myelin abnormality (354). Given the role of LXR in glucose homeostasis, although no direct evidence points toward a function of LXR in AD in the context of T2DM, it is still plausible that LXR-activation mechanisms are involved in the elimination of diabetes and the treatment of AD.

E. Summarized mechanisms of LXR action in AD and perspectives

In summary, LXR appear to play a role in linking lipid metabolism to neuroinflammation in AD. LXR activation attenuates AD pathology, possibly through the following plausible mechanisms as depicted in Fig. 5. 1) Activation of LXR up-regulates ABCA1 expression, which inhibits neuronal Aβ secretion. 2) LXR modulate inflammation and increase the phagocytic capacity of microglia for Aβ engulfment. 3) ApoE is the direct target of LXR. LXR activate apoE transcription in astrocytes and microglia, which promotes Aβ degradation and clearance.

VI. Summary

The ability of LXR to reduce Aβ levels in the brain through regulation of lipid metabolism, and possibly neuroinflammation, makes them attractive targets for the treatment of AD. Additionally, activation of LXR seems to have beneficial effects on glucose control in T2DM mouse models, suggesting a plausible role for LXR in the treatment of AD in the context of diabetes. However, systemic administration of synthetic LXR ligands markedly increases hepatic lipogenesis and plasma TG levels, which constitutes major obstacles. On the other hand, a specific, targeted action on bone marrow stem cells and on the CNS has to be taken into serious consideration as an alternative mode of delivering such agonists to circumvent the undesirable systemic effects. Given the divergent results of apoE and differences between mice and humans, there are thus still unresolved questions to be addressed. Much work will be necessary in the future to further clarify the exact role and potential of LXR in AD.

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