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Cholesterol Metabolism in Aging and Age-Related Disorders

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Keywords

aging, age-related neurological disease, Alzheimer's disease, cholesterol, microglia, neurons

Abstract

All mammalian cell membranes contain cholesterol to maintain membrane integrity. The transport of this hydrophobic lipid is mediated by lipoproteins. Cholesterol is especially enriched in the brain, particularly in synaptic and myelin membranes. Aging involves changes in sterol metabolism in peripheral organs and also in the brain. Some of those alterations have the potential to promote or to counteract the development of neurodegenerative diseases during aging. Here, we summarize the current knowledge of general principles of sterol metabolism in humans and mice, the most widely used model organism in biomedical research. We discuss changes in sterol metabolism that occur in the aged brain and highlight recent developments in cell type–specific cholesterol metabolism in the fast-growing research field of aging and age-related diseases, focusing on Alzheimer's disease. We propose that cell type–specific cholesterol handling and the interplay between cell types critically influence age-related disease processes.

Contents

INTRODUCTION

The world population has steadily increased from approximately 2.5 billion in 1950 to more than three times that value today. In industrial countries, this increase is coupled to a shift in the age distribution of the population, with an increment of the median age by almost nine years and a prolonged life expectancy of almost 14 years (Roser et al. 2013). In the United States, the Census Bureau estimated a 1.5-fold rise in the population aged 65 years and older within the next 30 years (GBD 2016 Neurol. Collab. 2019). Despite improved medical care, the health span, which designates the period of life that is free of serious, life-threatening disease, has not increased to a similar degree as the life span. Consequently, the total burden of disease remains highest in people aged 70 years or older (Roser et al. 2021). Hence, in light of these demographic changes, the development of concepts for managing age-related diseases is of pivotal medical, socioeconomic, and financial importance.

Aging is a process characterized by gradual decline of physiological pathways leading to decreasing physical and mental abilities. The underlying causes relate to telomere shortening, chronic oxidative stress, accumulating genetic damage, and epigenetic modifications over time. The pathways that lead to cellular senescence involve metabolic defects, including mitochondrial dysfunction; impaired turnover processes such as autophagy, proteostasis, reduced protective, and regenerative capabilities; and ceasing efficacy of endogenous repair processes. Each of these factors contributes to cellular senescence and raises the risk of developing age-related diseases. Accelerated aging, characterized by declining biological processes at a rate that exceeds the chronological age, is generally associated with one or more illnesses. The opposite, a condition of slowed physiological decline with prolonged health span and improved quality of life, has been termed healthy aging. Multidisciplinary investigations of the elderly aim to understand the mechanisms of resilience against physiological and cognitive decline (Beker et al. 2020, Zeng et al. 2017).

The most common aging-associated diseases comprise cardiovascular disorders, cancer, skeletal disorders, and vision defects in addition to neurodegenerative disorders. These pathologies can influence each other by acting as a comorbidity or risk factor; for example, cardiovascular pathology can aggravate the expression of age-related neurodegenerative disorders (Song et al. 2021). Neurodegenerative disorders are recognized as a major cause of death and disability (GBD 2016 Neurol. Collab. 2019).

Advanced neurodegenerative pathology is associated with neuronal loss and brain atrophy and presents with progressive dysfunction. In contrast to peripheral organs such as the liver (Heinke

et al. 2022), the nervous system is most susceptible to these age-related illnesses because of the limited ability of cell renewal (Reu et al. 2017, Yeung et al. 2014). However, the initial mild cognitive decline of the aging brain is caused rather by loss of connectivity and plasticity (Bishop et al. 2010). The pathological correlates of this declining brain functionality are disturbances of synaptic transmission and myelinated fibers (Bishop et al. 2010). At present, there are no curative or preventive medications available for neurodegenerative disorders.

The major age-related neurodegenerative disorders comprise stroke, Parkinson's disease, and dementia. At least 44 million people worldwide are living with dementia, the most common form of which is Alzheimer's disease (AD), accounting for 60–80% of the cases. Especially in Japan, the prevalence of dementia has increased dramatically within the last few decades (Dodge et al. 2012, Ohara et al. 2017). Here, in addition to the extremely expanded percentage of aged people in the Japanese population (median age 22.3 years in 1950 compared to 48.2 years in 2020) (Roser et al. 2013) and the improved survival of dementia patients, this development has been linked to the transition of Japanese people to a Western lifestyle (Grant 2014). Western-type nutrition correlates with the risk of developing dyslipidemia, obesity, and vascular morbidities such as atherosclerosis that often involve dysregulated cholesterol metabolism.

The role of cholesterol metabolism in neurodegenerative disorders is the subject of a fast-growing field of biomedical research. In this review, we therefore discuss a selection of recent developments. We first introduce cellular cholesterol homeostasis and compare peripheral and central nervous system (CNS) cholesterol metabolism in health and disease. Finally, we address cellular contributions of cholesterol metabolism to the age-related neurodegenerative disease AD.

CHOLESTEROL METABOLISM DURING HEALTH

Cellular Cholesterol Homeostasis

Cholesterol is critically involved in the biophysical properties of mammalian membranes, including their stability, fluidity, tightness, and semipermeable nature. Each cellular membrane has its specific content of cholesterol; while plasma membranes contain the highest levels of this essential sterol, internal membranes such as the endoplasmic reticulum (ER) have a low cholesterol content (Ikonen & Zhou 2021). Cholesterol molecules are not uniformly distributed in cellular membranes but are enriched together with sphingolipids and gangliosides in certain membrane regions, termed membrane lipid rafts. Ranging from 10–200 nm in size, these microdomains harbor proteins that segregate to these specialized membrane stretches and serve as functional hubs for many physiological processes such as intracellular signaling. In addition to these classical membrane lipid rafts, membrane contact sites between mitochondrial and endoplasmic reticulum membranes (MAMs) show raft-like enrichment of lipid components, including cholesterol (Vance 2014). Whether other types of this diverse family of membrane contact sites, for example, between the ER and the plasma membrane, between endo/lysosomes and mitochondria, or between lipid droplets and mitochondria, also enrich cholesterol and share similar physical and biochemical properties is currently unknown. MAMs contain proteins involved in cholesterol metabolism such as sterol O-acyltransferase 1 (SOAT1) (Lak et al. 2021), which synthesizes the storage form of cholesterol, cholesterol esters. Membrane contact sites have been associated with essential roles in cellular physiology, including autophagy, signaling, calcium homeostasis, lipid synthesis, and lipid transport, enabling the dynamic nature of the lipid content of cellular membranes. In addition, not only nonvesicular but also vesicular intracellular transport processes have been linked to the maintenance of cholesterol homeostasis (Luo et al. 2019).

Cellular cholesterol levels are maintained by tightly regulating cholesterol synthesis, uptake, internal storage, and release. This complex regulatory system involves a number of sterol-sensing

proteins, transcriptional control by the sterol responsive element binding protein 2 (SREBP2) transcription factor, and posttranscriptional and posttranslational regulation and has been the topic of excellent recent reviews (Brown et al. 2018, Ikonen & Zhou 2021). Central to the transcriptional regulation of cholesterol synthesis is the sterol-sensing SREBP cleavage-activating protein (SCAP) located in the ER. When cellular cholesterol levels fall below a critical threshold, SCAP escorts premature SREBP2 to the Golgi for proteolytic processing and activation of its transcriptional activator function. Notably, although the mechanisms of cellular cholesterol homeostasis are well known, how the individual level of fasting blood cholesterol concentration is regulated remains enigmatic. Excess cellular cholesterol is either released from the cells or stored intracellularly as cholesterol esters in lipid droplets.

Cellular cholesterol handling is linked to lysosomal and autophagosomal catabolism pathways. Egress of cholesterol from lysosomal membranes is a prerequisite for final degradation of internalized material. Cholesterol exit from lysosomes is mediated by the Niemann-Pick C1 and C2 (NPC1 and NPC2) proteins and membrane contact sites to other organelles (Lu et al. 2021, Trinh et al. 2020). Loss of NPC proteins causes lysosomal accumulation of cholesterol, which can be rescued by cyclodextrin-mediated cholesterol extraction or by artificial membrane tethering (Abi-Mosleh et al. 2009, Höglinger et al. 2019). Genetic defects in NPC proteins lead to the development of the fatal lysosomal storage disorder Niemann-Pick type C disease that also manifests with neurodegeneration. Autophagy is the predominant cellular pathway of nonspecific degradation of macromolecular material, including organelles, lipid droplets, and protein aggregates such as β-amyloid (Barbero-Camps et al. 2018). During autophagic degradation, intracellular material is sequestered into double-membrane vesicles termed autophagosomes that finally fuse with lysosomes for cargo turnover. Cholesterol depletion, as well as loading, induces autophagosome formation in cell culture but might slow the flux rates (Barbero-Camps et al. 2018, Shapira et al. 2021). Of note, the miR17–92 microRNA cluster regulates lipid and cholesterol metabolism, including autophagy (Estfanous et al. 2021).

Central Nervous System Versus Peripheral Cholesterol Metabolism

The body meets its cholesterol demand from nutrition-derived sources and cellular synthesis. Under normal conditions, nutrition accounts for approximately 25–30% of the body's cholesterol. Endogenous cholesterol synthesis is adjusted to the amount of cholesterol intake. Because of its lipophilicity, cholesterol is not transported freely in the circulation but bound to either blood proteins such as albumin or contained in lipoproteins, which carry free cholesterol in the limiting layer and esterified cholesterol in their lipophilic core. Several classes of lipoproteins are responsible for cholesterol transport in the circulation.

Low-density lipoprotein (LDL) predominantly mediates cholesterol transport from the liver to other organs, while high-density lipoprotein (HDL) mediates transport from the organs back to the liver, a process called reverse cholesterol transport (Gordon et al. 2015). These two major classes of lipoproteins, which are both essential for human health, differ in size, density, and lipid, protein, and apolipoprotein composition. Of note, although cholesterol has been designated "bad cholesterol" or "good cholesterol" when transported by LDL or HDL, respectively, the cholesterol molecules are identical.

LDL particles and related lipoproteins contain apolipoprotein B100 (ApoB100), which binds to the family of lipoprotein receptors, with low-density lipoprotein receptor (LDLR) and low-density lipoprotein–related protein 1 (LRP1) as the most prominent members. Binding triggers the uptake and clearance of LDL in lysosomal compartments. In contrast, HDL contains mainly apolipoprotein A-I (ApoA-I) and releases cholesterol esters without internalization, which involves

either scavenger receptor (SR-BI) or extracellular lipases. Lipidation of HDL occurs via efflux ATP-binding cassette (ABC) transporters such as ABCA1 (Rohatgi et al. 2021).

Apolipoprotein E (ApoE) is contained in several lipoprotein particles such as chylomicrons, the subset of ApoB-containing very-low-density and intermediate-density lipoproteins. HDLs carry only a minor fraction of ApoE. In humans, three ApoE alleles have been found, termed *APOE2*, *APOE3*, and *APOE4*. Although the underlying polymorphisms comprise only two point mutations, the resulting ApoE variants show strongly altered cholesterol transport capabilities (Chen et al. 2021b). Independent of age-related trajectories, lifelong total serum cholesterol levels of *APOE2* carriers are approximately 10 mg/dL below those of *APOE4* carriers (Downer et al. 2014). In comparison to APOE2 or APOE3, APOE4-containing lipoproteins carry low levels of cholesterol. The *APOE4* allele is a recognized risk factor for diseases with vascular contributions, including cardiovascular disease and dementia, particularly AD (Chen et al. 2021b). In contrast, the *APOE2* allele is associated with decreased risk to develop AD.

Lipoprotein subclasses have been identified based on their size and protein composition. This likely also reflects functional differences, but the specific role of each subclass is not well understood. In healthy adult individuals, HDL contains approximately 20–30% of the blood cholesterol, whereas LDL contains 60–70%. Adding a layer of complexity, lipoprotein particles of different classes vividly exchange apolipoproteins and lipids, including cholesterol esters, and the process is mediated by the cholesterol ester transfer protein in humans. Due to the absence of this enzyme in rodents, separation of lipoprotein classes is stricter, resulting in approximately 60% of plasma cholesterol being associated with HDL (Gordon et al. 2015). The sterol backbone of cholesterol cannot be enzymatically disassembled in mammals. Consequently, degradation of cholesterol is achieved after conversion to bile acids, which is followed by biliary excretion.

Pharmaceutical interventions affecting cholesterol metabolism target the absorption of dietary and biliary cholesterol in the small intestine, the hepatic clearance of LDL, and the reverse cholesterol transport (Herink & Ito 2000). In addition, cholesterol synthesis is inhibited by statins. These cholesterol-lowering drugs have been used for decades and are the most commonly prescribed drugs worldwide. In the United States, approximately 30% of adults, and almost 50% of people aged 75 years or older, take cholesterol-lowering medications. Statins are prescribed to adults that present with elevated serum cholesterol and LDL cholesterol levels and increased risk for cardiovascular disease (Das et al. 2020, Gu et al. 2014). All these treatments efficiently interfere with different aspects of cholesterol metabolism. However, studies have also highlighted gradual endogenous compensation for pharmacological inhibition such as slightly but steadily increasing blood cholesterol and LDL cholesterol levels after long-term statin treatment (Dorsch et al. 2021, Xu et al. 2017).

The pool of cholesterol in the periphery is separated from the cholesterol in the nervous system. Normal concentrations of total cholesterol in plasma are around 200 mg/dL, and only 0.6 mg/dL are found in the cerebrospinal fluid (CSF) of adult healthy individuals (Koch et al. 2001). Furthermore, turnover rates of cholesterol strongly differ between the brain and circulation; in plasma, cholesterol is replaced within days, whereas the half-life of cholesterol in the adult brain is very long, approximately 1 year in mice and 5 years in humans (Ando et al. 2003, Wang & Eckel 2014). Brain cholesterol is almost completely independent of nutritional input, as the blood-brain barrier largely prevents entry of circulating cholesterol into the brain. As a consequence, local production of cholesterol in the brain meets almost the entire demand for this essential lipid in the CNS (Björkhem & Meaney 2004, Saher & Stumpf 2015). The rate of CNS cholesterol synthesis correlates with the expansion of cellular membranes, for example, to facilitate proliferation and neurite extension during embryonic development (Fünfschilling et al. 2012). The highest rate of CNS sterol synthesis, however, is coupled to the production of the lipid- and cholesterol-rich myelin

membranes. In humans, myelination commences in the second trimester of gestation and continues for several years postnatally, whereas CNS myelination in rodents largely takes place early postnatally (Saher et al. 2005, Wilson et al. 2021). In adult brains of rodents, approximately 70–80% of the cholesterol is found in myelin (Björkhem & Meaney 2004). Myelin membranes are produced by oligodendrocytes that extend cell processes around axons to insulate and protect these neuronal projections. Myelin membranes and cholesterol are intrinsically tied to each other, as the availability of cholesterol is rate limiting for myelination (Camargo et al. 2017, Saher et al. 2005). Surprisingly, oligodendrocyte differentiation can be promoted by a short pulse of statin treatment in vitro (Miron et al. 2007), pointing to the complex relationship between transcriptional control of oligodendrocyte differentiation and cholesterol synthesis. In the brain, other sterols, such as 8,9-unsaturated sterol synthesis intermediates and 24,25-epoxycholesterol, have been linked to enhanced differentiation of oligodendrocytes (Allimuthu et al. 2019; Hubler et al. 2018, 2021), but the mechanism of these (presumably) signaling events remains enigmatic. Genetic deletion of SREBP or SCAP in astrocytes mediated by a human GFAP-Cre driver line also affects myelination and causes neurological defects (Camargo et al. 2017, Ferris et al. 2017, van Deijk et al. 2017). In addition, peripheral lipid metabolism is also severely perturbed in conditional SREBP mutants, but the causing mechanism remains unclear (Ferris et al. 2017).

After myelination has been largely accomplished, the rate of cholesterol synthesis drops to a low steady-state level in the adult CNS. Cholesterol synthesis by astrocytes is highest in the adult CNS, but presumably every cell type continues to contribute to cholesterol homeostasis by low-level endogenous synthesis (**Figure 1a**). Notably, inactivation of cell type–specific cholesterol synthesis in adult mice is endogenously compensated; targeting the squalene synthase, the first enzyme of the pathway devoted to sterol synthesis, in neurons, astrocytes, oligodendrocytes, or microglia of adult mice does not cause brain pathology (Berghoff et al. 2021a,b; Fünfschilling et al. 2012). Lipoprotein-mediated transport of cholesterol also exists in the CNS. Although similar to the circulation, the complexity of this intercellular transport system in the CNS remains far below that of the periphery. ApoE is the major apolipoprotein in the CNS; other apolipoproteins such as ApoA-I, ApoD, and ApoJ have also been found in the human brain (Wang & Eckel 2014). Although lipoprotein subclasses also exist in the CNS, all lipoprotein particles therein are most similar to plasma HDL. Astrocytes are the major producers of cholesterol in the adult CNS and also synthesize the majority of the CNS ApoE (Dietschy 2009). Thus, astrocytes likely provide cholesterol to other brain cells via lipoprotein-mediated transport. However, virtually all brain cells synthesize ApoE, ABC transporters, and lipoprotein receptors and are thereby able to release, lipidize, and internalize lipoproteins. The complexity of lipoprotein-mediated cholesterol transport in the CNS is not well understood. Excretion of cholesterol from the CNS across the blood-brain barrier requires oxidative modification of the cholesterol side chain to increase hydrophilicity. This process leads to the formation of the major and brain-specific CNS oxysterol 24S-hydroxycholesterol. This conversion, which is mediated by the enzyme CYP46A1, occurs mainly in a subtype of neurons under physiological conditions. Other oxysterols in the CNS comprise 27-hydroxycholesterol and 25-hydoxycholesterol, whose synthesis can occur in all CNS cell types. Another export pathway might involve lipoprotein-mediated transport across the blood-brain barrier with unknown specifications (Xie et al. 2003).

In addition to enzymatic production, autooxidation can lead to the formation of oxidized derivatives of cholesterol. Several oxysterols have been linked to signaling cascades. For example, certain oxysterols are known endogenous activators of liver X receptor (LXR) of the nuclear receptor family (Y. Wang et al. 2021). LXR signaling mediates the release of cellular cholesterol to lipoproteins via ABC transporters. Proinflammatory processes are also dampened by this signaling pathway (Spann et al. 2012). In addition to oxysterols, LXR signaling can be activated by
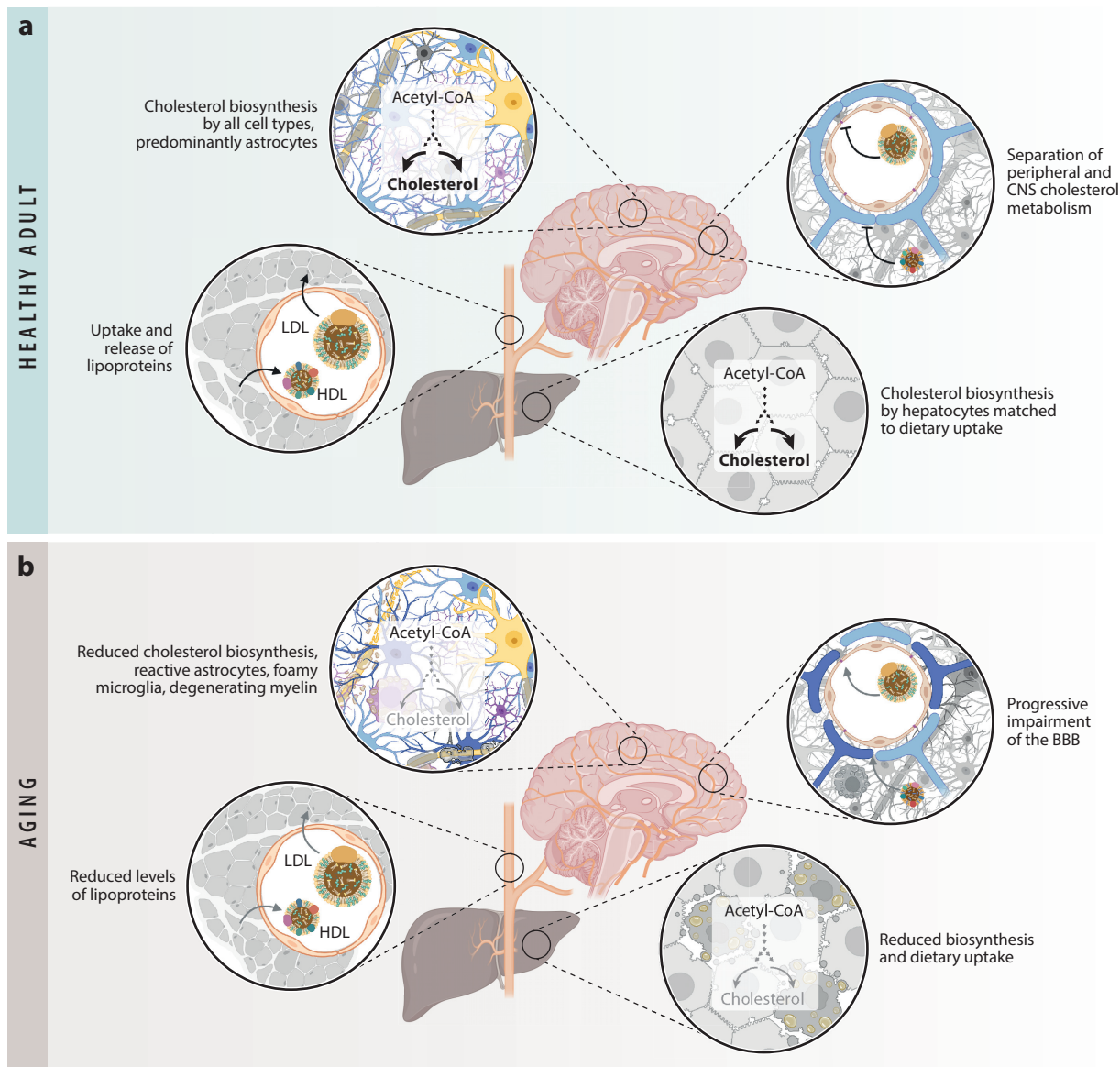
Figure 1

Cholesterol metabolism in the healthy adult and aging-related changes. (*a*) In healthy adult individuals, circulating cholesterol is regulated by hepatic synthesis that is matched to dietary uptake. The complex cholesterol biosynthesis pathway starts from acetyl coenzyme A (acetyl-CoA), a central metabolic intermediate. Circulating cholesterol is predominantly contained in lipoproteins. Low-density lipoproteins (LDLs) mediate cholesterol transport to recipient organs, whereas high-density lipoproteins (HDLs) mediate the reverse cholesterol transport back to the liver. Cholesterol metabolism in the body is separated from that of the brain because of the shielding function of the blood-brain barrier (BBB). Consequently, all cells of the adult brain, but predominantly astrocytes, synthesize cholesterol. In addition, central nervous system (CNS) lipoproteins mediate intercellular transport of cholesterol and other lipids. (*b*) With aging, several aspects of cholesterol metabolism change. Lower circulating cholesterol levels are caused by reduced dietary uptake and hepatic synthesis, potentially due to dysfunctional hepatocytes. Cholesterol synthesis also decreases in the brain. Progressive degeneration of CNS processes and the diminishing ability to turn over debris lead to activated astrocytes and to increasing densities of foamy-appearing microglia. The resulting low-level but chronic inflammation contributes to vascular defects and the gradual impairment of the BBB, which further perturbs CNS cholesterol metabolism. Figure adapted from images created with BioRender.com.

certain sterol synthesis intermediates such as squalene and desmosterol (Berghoff et al. 2021b, Muse et al. 2018). Linked to LXR signaling, the oxysterol 25-hydoxycholesterol activates the nucleotide-binding oligomerization domain, leucine-rich repeat, pyrin domain-containing protein 3 (NLRP3) inflammasome (Duewell et al. 2010, Jang et al. 2016, Y. Wang et al. 2021). Another mechanism involves SCAP, whose glycosylation leads to the disruption of cholesterol feedback regulation and foamy accumulation of lipids in a macrophage cell line (Zhou et al. 2013). Increased levels of keto-cholesterol, another oxygenized derivative of cholesterol that is used as a marker for oxidative stress and by itself damages cell membranes, have been found in age-related diseases (Anderson et al. 2020). As a major driver of aging and neurodegeneration, mammalian target of rapamycin (mTOR) signaling integrates cellular energy metabolism with stress and autophagy-mediated degradation (Liu & Sabatini 2020). SREBP transcription factors are targets of mTOR, and lysosomal cholesterol activates mTOR signaling, revealing that the cholesterol-mTOR axis plays a central role in cellular homeostasis (Liu & Sabatini 2020). However, the complex interplay of the regulation of cholesterol synthesis, brain cell differentiation, and inflammation, especially in the aging brain, remains largely unsolved.

CHOLESTEROL METABOLISM DURING AGING AND IN AGE-RELATED NEUROLOGICAL DISEASES

Cholesterol Metabolism During Aging

Serum cholesterol and LDL cholesterol levels increase until adulthood and decline later in life after adjusting for confounding factors such as environmental and hormonal factors, socioeconomic status, and cholesterol-lowering medication (Downer et al. 2014, Silbernagel et al. 2010, Tilvis et al. 2011). This age-related decline of cholesterol levels is accompanied by both reduced dietary absorption and hepatic synthesis (**Figure 1***b*). Hypercholesteremia and obesity in middle-aged individuals are known to associate with the development of dementia (Dai et al. 2021), which is likely also promoted by vascular defects. Surprisingly, in aged individuals, low plasma cholesterol, low synthesis/uptake, and even low LDL cholesterol have been associated with poor health and mortality (Lv et al. 2015, Schupf et al. 2005, Silbernagel et al. 2010, Tilvis et al. 2011). Although controversial, the risk of developing side effects from cholesterol-lowering medication might be increased in aged people (Alsehli et al. 2020, Thompson et al. 2016, Ward et al. 2019). Moreover, survival beyond 90 years of age was linked to rising plasma cholesterol levels during old age (Downer et al. 2014). Higher LDL levels predicted healthy survival in a study with women aged 68 years or older that survived their ninetieth birthday (Maihofer et al. 2020), challenging the bad reputation of elevated cholesterol and LDL-cholesterol in elderly people. The link between blood cholesterol and cellular senescence is likely indirect, as the HDL efflux capacity in leukocytes did not correlate with telomere length, a marker of senescence, in elderly compared to middle-aged subjects (Zimetti et al. 2018). As low circulating-cholesterol levels have been linked to fatal liver cirrhosis (Janičko et al. 2013), it is possible that gradually impairing liver function could be the underlying cause of this association between blood cholesterol and longevity.

As in plasma, cholesterol levels and synthesis rates decrease in the adult and aging brain (Boisvert et al. 2018, de la Fuente et al. 2020, Thelen et al. 2006) (**Figure 1***b*). Whether this trend reverses in very aged healthy brains, as observed in the circulation, is unknown. The reduced rate of brain cholesterol synthesis and presumably the reduced supply by astrocytes (Boisvert et al. 2018, Habib et al. 2020) go along with a decline in the extent of myelination and/or with reduced cholesterol content in myelin membranes (Stommel et al. 1989, Thelen et al. 2006). It is possible that in the aging brain, myelin serves as an alternative source of this essential lipid to maintain brain cholesterol homeostasis. Contributing to the increasing loss of myelin, the rate

and efficiency of myelin repair decrease with age (Cantuti-Castelvetri et al. 2018, Franklin et al. 2021). This decrease has been attributed to inefficient recycling of lipids and cholesterol from the phagocytosing microglia/macrophages (Berghoff et al. 2021b, Cantuti-Castelvetri et al. 2018). The density of synapses, which also contain high cholesterol levels, also declines during aging. Reduced cholesterol content in cell membranes likely affects membrane dynamics and subsequently endocytosis and exocytosis events (Burrinha et al. 2021). Chronic (low-grade) inflammation in the aged brain, also designated inflammaging, manifested in reactive astrocytes and microglia, likely also counteracts repair processes.

Impaired Cholesterol Homeostasis in Age-Related Neurological Disease

The dysregulation of sterol metabolism in age-related neurodegenerative diseases is dictated by disease-specific features, but some factors are shared between diseases, for example, certain single-nucleotide polymorphisms (SNPs), dysfunctional membrane domains, and vascular defects that critically promote brain diseases. The details of sterol metabolism in stroke as an intracranial atherosclerotic disease, Parkinson's disease, and myelin-related disorders such as multiple sclerosis are covered by excellent recent reviews (Berghoff et al. 2022, Groenen et al. 2021, Pingale & Gupta 2021). In the following paragraphs, we focus on the interplay between sterol metabolism, aging, and AD.

AD symptoms begin with minor disorientation and language perturbations that progress to confusion, loss of speech, and memory loss. AD also often presents with sleep disturbances and mood changes gradually affecting behavioral and social skills. Disease progression also leads to a broad range of neuropsychiatric symptoms such as depression, anxiety, delusions, or aggressiveness. Due to the initially subtle clinical changes that can hardly be distinguished from normal aging and the oftentimes slow rate of disease progression in the preclinical and prodromal stages of AD, disease onset can precede the diagnosis of dementia by decades (Vermunt et al. 2019). However, clinical deterioration can also progress fast, especially in the terminal stage of the disease. The duration of AD stages shortens with age, and aging is the strongest risk factor for AD (DeTure & Dickson 2019, Vermunt et al. 2019).

The two cardinal histopathological hallmarks of AD are the formation of intraneuronal aggregates of phosphorylated microtubule-associated protein tau in neurofibrillary tangles and extracellular deposits of amyloid in senile plaques. Loss of neurons and, more importantly, loss of synapses and synaptic plasticity are linked to initial cognitive deficits (Burrinha et al. 2021, Morrison & Baxter 2012, Peters et al. 2008a). Gliosis, neuroinflammation, and oxidative stress accompany brain damage (Edler et al. 2021). Biomarkers of preclinical AD include amyloid and tau levels in CSF and PET (positron emission tomography) analysis. On the biochemical level, homeostasis of calcium is disrupted, and there are disturbances of cholesterol and phospholipid metabolism and secondary effects on mitochondrial functions. These mitochondrial changes might involve dysfunction of membrane contact sites, as observed in mouse models of AD as well as in AD patients (Area-Gomez & Schon 2017). Moreover, dysregulated carbohydrate metabolism has been recognized as another early feature of dementia/AD (Bonvento & Bolanos 2021). Despite these neuropathological hallmarks of AD, the majority of patients suffer from age-associated comorbidities of dementia and cerebrovascular spectrums contributing to the variability of clinical presentations.

The understanding of the etiology of AD has developed from a pure neuronal pathology to a multifactorial disorder with many risk loci that involves all cell types in the brain and the immune system, although the number of risk loci is debated (Bellenguez et al. 2022; Johnson et al. 2020, 2022; Yang et al. 2022; Zhang et al. 2020a). Effective disease-modifying therapies of this complex
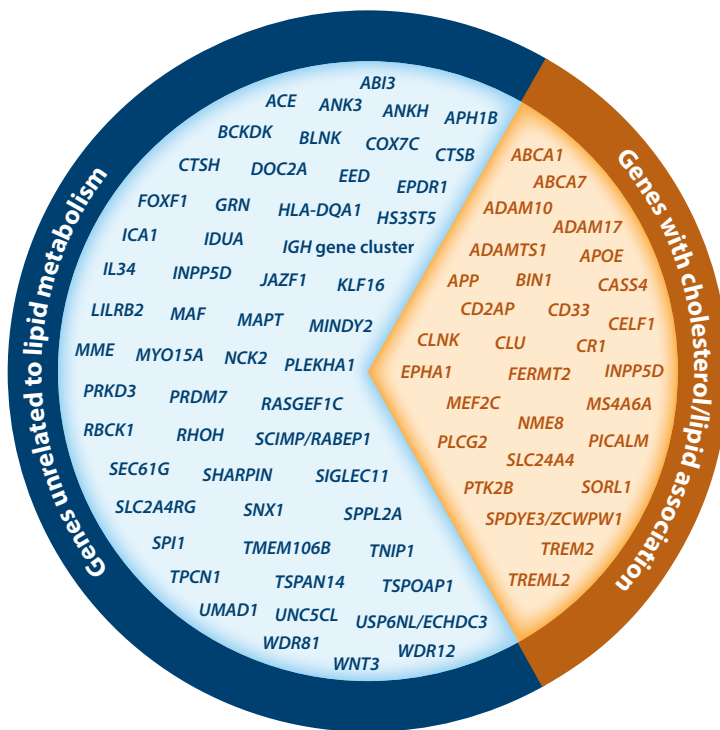
Figure 2

Genome-wide association studies and expression studies have revealed genes that are associated with
Alzheimer's disease (AD) risk (see also **Supplemental Table**). Approximately a third of those risk genes that
are known to date have been related to sterol and lipid metabolism (*orange*). These lipid- and cholesterol-
associated risk genes are predominantly implicated in cellular lipid/cholesterol release, transport, and uptake,
suggesting that these processes play a major role in AD pathogenesis.

disorder will require the individual targeting of multiple features of AD and comorbidities, likely
in personalized approaches.

AD and cholesterol metabolism are intimately linked to each other on several levels. This fact
is reflected by risk factors of AD, many of which, in addition to aging, relate to cholesterol/lipid
metabolism (**Figure 2**; **Supplemental Table**). The strongest risk factor for late-onset sporadic
AD is, in addition to age, the *APOE4* allele. Genome-wide association studies (GWASs) identified
further genes involved in cholesterol transport, including clusterin, phosphatidylinositol-binding
clathrin assembly protein (PICALM), ABCA7, and triggering receptor expressed on myeloid cells
2 (TREM2). In contrast, the rare Christchurch mutation in the *APOE3* gene is associated with
slowed AD progression, further strengthening the link between AD pathogenesis and cholesterol/
lipid metabolism. The recognized risk factors for familial AD are mutations in the amyloid precur-
sor proteins (APPs) and the APP-processing enzymes presenilin-1 and presenilin-2 that form the
γ-secretase complex. APP proteolysis occurs within cellular membranes and is closely linked to
neuronal cholesterol metabolism (see below). However, other lipid species, including the polyun-
saturated fatty acid docosahexaenoic acid, likely affect disease processes in aging and age-related
diseases (Grimm et al. 2017).

Hypercholesteremia in middle-aged individuals is an established risk factor for the incidence
and progression of AD (Dai et al. 2021). Plasma lipidomes, including cholesteryl ester levels from

AD cases, differ from age-matched controls and individual lipids differentially associated with SNPs in risk genes (Liu et al. 2021). Carriers of the *APOE4* allele have a fourfold- to 14-fold-higher (homozygous carriers) increased risk of developing AD. With respect to dyslipidemia, aging critically affects AD pathology, as a higher late-life body mass index (BMI) might protect against progression to AD (Sun et al. 2020), and a decreasing BMI increased the risk of developing amyloid pathology (Lane et al. 2021). In a meta-analysis, lipid-lowering medication either did not affect AD risk or suggested an increased risk of developing AD (Williams et al. 2020).

Moreover, conflicting findings with respect to sterol levels in the plasma, brain, and CSF of human patients (Dai et al. 2021, Jahn et al. 2021, Varma et al. 2021) suggest a complex relationship of sterol metabolism and AD. This is supported by GWASs and expression studies that found lipid/cholesterol-associated genes to be distributed over several clusters and pathways of lipid metabolism (Bellenguez et al. 2022, Johnson et al. 2022, Zhang et al. 2020a). Inferring from this and the cellular expression pattern of risk genes, we hypothesize that a distinct cell type–specific role in brain sterol metabolism could be a causative factor for AD pathogenesis.

CELLULAR CONTRIBUTIONS TO BRAIN AGING AND ALZHEIMER'S DISEASE

Initial cognitive decline in the aging brain occurs without loss of neurons. Rather, deteriorating neuronal performance, involving information processing and synaptic transmission, accounts for accumulating disabilities in the cortex and hippocampus of different species (Bishop et al. 2010, Peters et al. 2008a), but brain region–specific differences might exist. In contrast to neurons, oligodendrocyte densities increase with age in the visual cortex of rhesus monkeys (Peters et al. 2008b). Oligodendrocyte lineage cells are capable of cell renewal throughout life, accounting for the majority of proliferating cells in the adult healthy brain. However, increased age correlates with decreasing myelin internode lengths and accumulating myelin membrane abnormalities (Peters et al. 2008b). The degree of age-related myelin loss likely depends on the species and brain region. Myelin loss might even aggravate AD pathology in patients and amyloidosis models (Chen et al. 2021a, Depp et al. 2021, Zhang et al. 2020b). In the cortex of aging animals and humans, the astrocyte cell population remains stable, whereas microglial cell densities might increase, remain unchanged, or decrease (Boisvert et al. 2018, Edler et al. 2021, Peters et al. 2008b). Whether these discrepant findings of microglial cell population originate from varying degrees of brain insults during the prolonged life span remains unsolved. However, accumulating intracellular inclusions of proteins and lipids in cortical astrocytes, microglia, and neurons of aged healthy animals likely reflect a progressive impairment in being able to degrade waste products. The link between aging/senescence and waste degradation is further supported by the finding that rejuvenated aged microglia increased amyloid turnover in slice cultures (Daria et al. 2017). Moreover, genetic or pharmacological reinforcement of apoptosis of senescent glial cells in a tauopathy model prevented neurodegeneration and cognitive decline (Bussian et al. 2018). As the intracellular deposition of aggregated material, collectively designated as lipofuscin, increases in size and density in the context of degenerative CNS disease, turnover defects might contribute to the progressive functional exhaustion and senescence of cells, predominantly microglia (Safaiyan et al. 2016). The appearance of lipofuscin has been linked to failing catabolism via autophagosomes, which has been recognized as a key feature of senescent cells together with increased concentrations of reactive oxygen species and mitochondrial damage.

In the aging brain and in aged neurons, the cholesterol content decreases (Boisvert et al. 2018, de la Fuente et al. 2020, Thelen et al. 2006), likely disturbing the density of lipid packing as well as membrane fluidity and stiffness (Vanmierlo et al. 2011). These altered membrane properties

affect synaptic plasticity and could render membranes vulnerable to microruptures. Whether these changes in the lipid organization are part of the physiological aging process or reflect the adaption to age-related damage is still unknown. The moderate decrease of membrane cholesterol content in neurons might be linked to the increasing activity of CYP46A1 (Lund et al. 1999), which hydroxylates cholesterol, leading to the excretion of this lipid from the CNS. Increased esterification of cholesterol by the microsomal enzyme SOAT1 [also designated ACAT1, acyl-coenzyme A (acyl-CoA):cholesterol acyltransferase 1], which leads to cholesterol ester storage in lipid droplets, might also contribute to the aberrant handling of cholesterol in neurons.

In AD brains, compared to age-matched control individuals, transcripts of *CYP46A1* as well as cholesterol synthesis genes are decreased and, accordingly, steady-state brain cholesterol levels remain unchanged (Varma et al. 2021). However, indirect effects on neuronal cholesterol metabolism, mediated by ectopic expression of *CYP46A1* in AD astrocytes, are possible (Zarrouk et al. 2014). The importance of these cholesterol modifications for AD is further supported by improved amyloid pathology in APP-transgenic mice in which CYP46A1 activity was increased (Mast et al. 2017, van der Kant et al. 2019) or SOAT1 activity was decreased, either pharmacologically or genetically (Bryleva et al. 2010, Hutter-Paier et al. 2004).

Cholesterol is involved in both tau and amyloid pathogenesis in AD, and statin-mediated reduction of cholesterol levels generated mixed results (Dai et al. 2021), arguing in favor of cholesterol metabolism defects beyond its brain concentration. In AD brains and in the majority of rodent models of AD pathology, neurons are the major cell type that produces β-amyloid and hyperphosphorylated misfolded tau. They are vulnerable to the toxicity of accumulating β-amyloid and aggregating neurofibrillary tangles, leading to progressive neuronal death and brain atrophy. In addition to cell-autonomous defects, degenerating neurites in the vicinity of senile plaques and spatiotemporal propagation of tau misfolding lead to the spreading of pathogenic processes.

Every step in the generation of senile plaques from APP is linked to cholesterol. As this process has been the subject of many excellent reviews (Grimm et al. 2017), only some key facts are presented here. The β-amyloid-generating enzyme complex, including β- and γ-secretases, resides in membrane lipid microdomains of the plasma membrane and internal membranes. According to one theory, decreasing cholesterol levels in membrane microdomains enhance the probability that APP and secretases colocalize in internal membranes, increasing β-amyloidogenic over non-amyloidogenic APP cleavage. However, statin treatment can reduce APP processing in induced pluripotent stem cell neurons (Langness et al. 2021), suggesting that the reduction of neuronal cholesterol can have both beneficial and detrimental effects. Proteolysis products of APP comprise not only β-amyloid but also several carboxyterminal fragments (CTFs). The CTF C99 directly binds cholesterol, which could sequester cholesterol from internal membranes, further disturbing cellular cholesterol homeostasis (Barrett et al. 2012), which could lead to a vicious cycle of β-amyloid production and the disruption of cholesterol homeostasis. In addition, β-amyloid oligomerization and deposition has been linked to the cholesterol content of adjacent model membranes (Banerjee et al. 2021). Of note, in addition to APP processing, several signaling pathways that originate from raft microdomains are affected in aging cells, including insulin and tropomyosin receptor kinase B (TrkB) receptor signaling, further aggravating disease processes in AD neurons (Chow et al. 2019, Martin et al. 2008). Tau pathology is also linked to cholesterol metabolism as tau uptake, release into the neuronal cytosol, and seeding depend on reduced membrane cholesterol (Tuck et al. 2022). Despite many conflicting reports related to the cell biology of amyloidosis and tau pathology in cell culture and in rodent models, these findings suggest that these two hallmarks of AD pathology could be moderated if membrane cholesterol homeostasis was maintained.

In adult animals, neuronal cholesterol levels are regulated by cell-autonomous synthesis and uptake of ApoE-containing lipoproteins. In agreement with the *APOE4* variant being the major risk factor for sporadic AD, amyloid and tau pathologies have been linked to lipoprotein-mediated cholesterol transport in the brain. The large body of publications related to the complex relationship between ApoE biology and brain pathology has been reviewed elsewhere (Chen et al. 2021b). Briefly, the loss of ApoE causes vascular dysfunction and hypercholesteremia (Lane-Donovan et al. 2016). Although neurodegeneration is not a feature of ApoE knockout mice, these mutants suffer from synaptic defects and cognitive impairment in aged mutants (Fuentes et al. 2018). When ApoE knockout mice are challenged by amyloid pathology, the density of senile plaques is reduced without changing APP processing (DeMattos et al. 2004). In contrast, *APOE4* transgenic mice show exacerbated pathology, with respect to not only plaque load but also synaptic defects and neurodegeneration, similar to *APOE4* carriers. The *APOE4* allele also interferes with cellular cholesterol regulation and handling, including cholesterol secretion, esterification, and storage in lipid droplets (Fernandez et al. 2019). Moreover, the cellular source of ApoE has consequences for amyloid and tau pathologies (Henningfield et al. 2022, Mahan et al. 2022, C. Wang et al. 2021, H. Wang et al. 2021) and also for neuronal (hyper)activity (Konings et al. 2021), which is a feature of AD neurons. In light of the role of CYP46A1-mediated excretion of cholesterol from the CNS, these findings point to the flux of cholesterol between brain cells as a critical factor in AD pathology.

Aging-mediated attenuation of membrane cholesterol levels is likely not restricted to neurons but could directly affect the physiology of glial cells. Astrocytes, and even more so, microglia, whose surveilling functions depend on membrane dynamics, could suffer from age-related deficits in lipid homeostasis. Aging microglia progressively lose the motility of cell processes, and the density of microglia with resting/ramified morphology decreases. Moreover, their ability to migrate, a feature that is essential for many pathophysiological processes, also declines with increasing age. Together, these age-related changes reflect the loss of protective properties (Damani et al. 2011). Losing the ability to handle intracellular lipids is a key feature of aging microglia, leading to intracellular accumulation of cholesterol (Cantuti-Castelvetri et al. 2018, Marschallinger et al. 2020). Moreover, engaging CNS phagocytes with increased cholesterol turnover induced by a demyelinating insult exaggerated amyloidosis in mice (Depp et al. 2021). One central player in microglial phagocytosis and cholesterol handling is TREM2 (Gouna et al. 2021), which also plays a role in the clearance of β-amyloid (Lee et al. 2018, Nugent et al. 2020). Of note, in AD patients and mice, elevated levels of the lipid-associated miR17–92 cluster have been linked to the impairment of microglial autophagy of β-amyloid (Estfanous et al. 2021). Pharmacological support of autophagy coupled to suppression of mTOR reduces the amyloid burden in an AD model (Li et al. 2021). The aging microglial phenotype is accompanied by increasing cell activation, which is coupled to upregulation of proinflammatory mediators such as tumor necrosis factor (TNF) and downregulation of homeostatic markers such as transforming growth factor beta (TGF-β) (Provenzano et al. 2021). Expression profiling of microglia has led to the identification of disease- and age-associated molecular patterns (Depp et al. 2021, Provenzano et al. 2021, Safaiyan et al. 2021). Similarly, aging astrocytes partially lose the complexity of process arborization, accumulate autophagosomes, and show increasing defects of proteostasis (Lee et al. 2022, Orre et al. 2014), suggesting that the link between age-related defects and cholesterol metabolism is rather indirect in this cell type.

CONCLUDING REMARKS

Age-related alterations and cholesterol metabolism are intimately linked to brain homeostasis. The cholesterol level and the rate of de novo cholesterol synthesis decrease in the aging brain. Moreover, the subcellular distribution and handling of cholesterol and its derivatives are

affected, which also influence cellular and brain lipid metabolism. These alterations in cellular lipid metabolism are accompanied by progressive impairment of waste disposal, low-grade inflammation, and metabolic disturbances. All cell types of the brain show overlapping and distinct cholesterol-related alterations in the aging brain. Future studies of this rapidly growing research field will unravel the subcellular defects and causal relationship between dysfunctional cholesterol metabolism and cell activation, increased reactive oxygen species, and inflammation that promotes aging and the development of age-related pathologies.

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Errata

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