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Review

# Alzheimer's disease: Cholesterol a menace?

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ABSTRACT

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease manifested by cognitive and memory deterioration, culminating in a spectrum of neuropsychiatric disturbances and the impairment of daily activities. AD is a multifactorial disease with a range of contributing factors which includes genes and diet. The magnitude of AD is reflected in the loss of individuality of the affected person and in the terminal course through which the disease develops. In this review, we aim to provide a background on AD and the contribution of cholesterol in the etiology of Alzheimer's. Cholesterol seems to be intimately linked with the generation of amyloid plaques, which is central to the pathogenesis of AD. Although there are conflicting reports on the role of cholesterol in AD, majority of the studies point out the positive association of cholesterol with AD.



**Contents**



## 1. Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia and accounts up to 60–80 percent of dementia cases worldwide [28,129]. Alzheimer's disease was first reported more than a century ago by Dr. Alois Alzheimer in 1907 in a 51-year-old woman, who was his patient for 6 years [45,57,92]. Alzheimer's disease can be defined as a heterogeneous, progressive, irreversible, complex, multifactorial brain disease that destroys multiple cognitive skills. It is a slow fatal disease affecting one in ten over the age of 65 years [80,106,113,174]. It is assumed that by 2050, the world prevalence of AD will increase to 1 in 85 persons [15]. Incidence of AD shows strong positive association with increase in age and the prevalence increases exponentially around 65 years [66]. With the advancement in medical facilities and technology, the life expectancy and the average age of men have increased and as the world population

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ages, we face a looming gloomy global epidemic of AD [15]. Due to mutations and other genetic influence, rare cases of AD have been observed even in young individuals, as young as 30 years and are called as early onset Alzheimer and tend to be familial in onset. In this review, we are concentrating on late-onset sporadic AD. It is observed that the prevalence of Alzheimer's is higher in women than in men, and this might be due to difference in hormonal profile in women and might also be due the reason that women outlive men [7,54,62,81]. The disease progression is distinct and unique in affected persons and so the symptoms and the order of occurrence of the symptoms and its duration may vary. Generally the disease takes its toll very slowly, and the general life expectancy after the diagnosis varies from 3 to 10 years [168]. The socio-economic burden imposed by the cost intensive and time consuming patient care proves to be a matter of concern in AD management [62,66]. Progression of Alzheimer's is typically categorized into three different stages: early, middle and late stages. The early stage is marked by forgetfulness, changes in mood and behavior, and communication difficulties. An individual's cognitive and functional abilities are greatly affected in the middle stage of Alzheimer and continue to deteriorate. They might require assistance to perform various daily tasks. In the late stage, round the clock attention and care is entailed as the individual looses most of the cognitive and communicative skills. The patient finally succumbs to death. A supportive care, which focuses on highest quality of life possible and comfort along with physical, emotional and spiritual support is expedient [79,114,115].

Although the disease has been identified nearly a century ago, it was during the 1970s that the scientific community started getting more interested in this field. A complex cascade of events contributes to the manifestation of the disease [20] which is influenced by various genetic [125,154] and non-genetic factors. Few of the non-genetic factors contributing to Alzheimer's include head trauma, hypertension, diabetes mellitus, hypercholesterolemia, history of stroke, dietary habits and educational levels [31,44,69,134]. There is accumulating evidence suggesting the role of cholesterol in AD [55,117,134] and this link is now being thoroughly investigated by researchers. The current available drugs for Alzheimer's are mainly symptomatic and do not tackle the underlying pathology of AD. They provide only temporary symptomatic relief and are useful only in mild-moderate cases [28].

## 2. Pathology of Alzheimer's disease

The major histopathological manifestations in AD brain are the extracellular amyloid plaques (also known as senile plaques) and intracellular neurofibrillary tangles [105,145], which occur in concert with secondary developments like oxidative stress, lipid peroxidation, inflammation, excitotoxicity of glutaminergic neurons, vascular toxicity, production of proinflammatory cytokines by glial cells and initiation of apoptotic cascade [28,123]. These changes correlate with the synaptic alterations, cholinergic deficits, mitochondrial dysfunction and neuronal cell death observed in AD [52,66]. Plaques and tangles accumulate in the brain, leading to shrinkage of neurons and neuronal loss, which eventually leads to cerebral atrophy [66].

### 2.1. Amyloid precursor protein and amyloid beta plaques

Amyloid plaque which is considered to have a crucial role in AD are aggregates of amyloid β (Aβ) peptides of 4 kDa with 39–43 amino acid residues [105]. They are deposited in the brain parenchyma and cerebrovasculature leading to the loss of synapse and neurotoxicity [52,126,174]. The Aβ plaques are formed by the successive proteolytic processing of amyloid precursor protein (APP). APP is an integral, single, transmembrane protein with 695–770 amino acids, transported from the endoplasmic reticulum to the cell surface through the secretory pathway [154]. It belongs to an evolutionarily conserved family of Type I transmembrane proteins and has a large extracellular hydrophilic N terminal, a single 23-amino acid transmembrane domain and a small cytoplasmic C-terminal [2,52]. The physiological role of this ubiquitously expressed protein includes the axonal vesicular trafficking and is concentrated in the synapse of neurons. APP is insinuated as a regulator of synapse formation and neural plasticity. APP is proteolytically cleaved by three different secretases – α, β and γ (Fig. 1), and the choice of secretase is vital in Alzheimer development [144,170].

The proteolytic processing of APP can be either via non-amyloidogenic pathway or amyloidogenic pathway. The α and β secretase have cleavage sites in the extracellular domain of APP [52]. The non-amyloidogenic pathway involves the sequential cleavage of APP by α-secretase, within the amyloid peptide domain and subsequently by γ-secretase producing a secretory APP (sAPPα) segment and a membrane bound C α-terminal fragment (α-CTF). α-CTF on cleavage by γ-secretase generates a truncated non-amyloidogenic peptide (p3) and this precludes the generation of amyloid beta fragments. The sAPPα activates a putative receptor on the neuronal membrane, leading to a series of reaction, which opens the $K^+$ channels and activates the nuclear transcription factor – NFκB, leading to cell survival promoting signals [91,98,158].

In the amyloidogenic pathway, β secretases (BACE) cleaves the APP at the C terminus releasing sAPPβ and a membrane bound C β-terminal fragment (β-CTF). The ubiquitous multimeric γ-secretase cleaves β-CTF at different cleavage sites leading to the genesis of amyloidogenic Aβ fragments of varying sizes. The main variants are the Aβ40 and Aβ42 peptides with 40 and 42 amino acids respectively. Aβ42 are highly hydrophobic due to the presence of leucine at 41st and valine at 42nd positions at the C-terminus of the peptide and they tend to form aggregates more easily under conditions like oxidative stress, resulting in the fabrication of amyloid plaques [52,105]. The aggregated extracellular β-amyloid plaques lead to membrane lipid peroxidation, which results in the disruption of $Na^+/Ca^+$ channels and glucose uptake by the cell. These changes promote apoptosis. Intraneuronal amyloid fragments are highly insoluble and toxic, and appear to have a hand in deregulated calcium homeostasis, apoptosis, generation of pores in cell membrane, activation of complements and generation of free radicals, although the exact mechanism is not known [2,137]. The aggregated or polymerized amyloid fibers have highly secondary β sheet structure [159]. The intra-cellular APP domain (AICD) is released into the cytosol, independent of the type of secretase which cleaves APP, and they migrate to the nucleus, where they are supposed to take part in gene transcription [67,152].

For long, Aβ fragments were considered as products of cellular damage, due to which it was thought to be released, but in 1992, it was established to be a normal by-product of cellular metabolism [47]. A delicate balance is maintained between the rate at which amyloid is formed and its clearance. Amyloid deposits can be reabsorbed and organ dysfunction reversed if the synthesis of amyloidogenic protein is shutdown. The re-absorption mechanism is not clearly known, but is postulated to be related to phagocytosis by microglia [93]. Various reports have supported the amyloid degrading capability of neprilysin (NEP), insulin degrading enzyme (IDE) and angiotensin converting enzyme (ACE) [21]. Soluble Aβ can cross the blood–brain barrier (BBB) through receptor for advanced glycalation end products (RAGE) and Low density lipoprotein receptor-related protein (LRP) and these fragments are systemically cleared from the blood [173,174]. Studies by Koudinov and Berezov report that amyloid is not a 'neurotoxic junk', but is essential for normal synaptic function and plasticity [74].

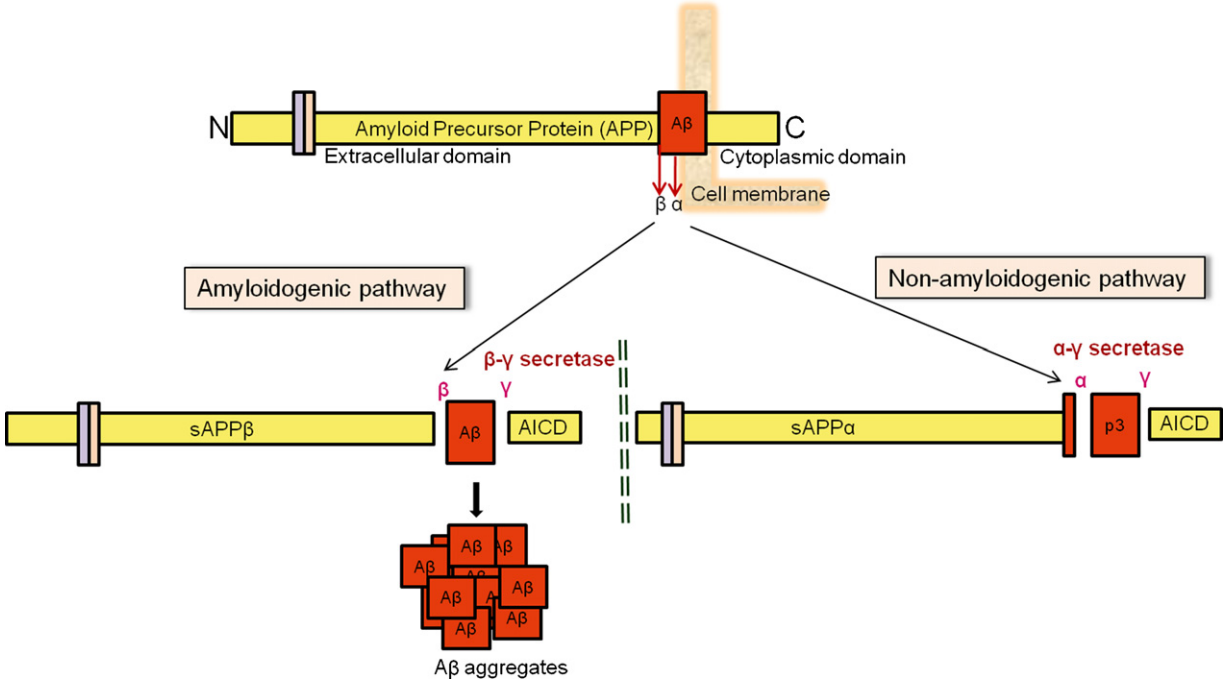


**Fig. 1.** Proteolytic processing of amyloid precursor protein. Processing by β–γ secretase follows the amyloidogenic pathway forming Aβ aggregates while the α–γ secretase activity ends in non-amyloidogenic processing.

### 2.2. Tau phosphorylation

Tau proteins are neuronal micro-tubule associated proteins (MAPs), which on abnormal phosphorylation produces the intracellular neurofibrillary tangles in AD. Tau proteins help in regulating the microtubule dynamics, axonal transport and neuritic outgrowth and are mainly found in the axons. They are formed by the alternative splicing of mRNA and help in establishing functional polarity of neurons. The functional properties are regulated by site-specific phosphorylation which can occur at multiple sites. In AD, tau proteins undergo abnormal phosphorylation leading to the accumulation of tau proteins which manifests as insoluble neurofibrillary tangles, disrupting the normal functioning of the protein. The hyperphosphorylated tau disrupts normal microtubule binding, leading to the loss of axons and defective neuronal communication and later to neuronal loss [64,86].

### 2.3. Mitochondria and Alzheimer's disease

Mitochondria, "the power house of the cells" are centers of complex metabolic reactions which meet the energy requirements for the cell. Defective mitochondria do not meet the energy requirements of the cell, but are damaging to the cell due to its efficient production of reactive oxygen species (ROS), leading to cellular oxidative stress [172]. Severe mitochondrial dysfunction results in cell death. Energy requirement of the brain is dependent on aerobic metabolism and this makes the cerebral neuronal cells the most vulnerable target cell population in the event of respiratory chain failure [99]. Brain aging produces typical symptoms of neurodegenerative disorders including neuronal loss, synaptic dysfunction and loss of synapse. Moreover, aging results in the accumulation of mutations in the mitochondrial DNA [96,110]. According to the review by Atamna and Frey [4], mitochondrial dysfunction has three consequences on AD: defective energy metabolism, oxidative damage and metabolic consequences like low regulatory heme. Apart from this, an overall decline of mitochondrial number and function is observed in the brains of patients with AD when compared to controls. Due to the structural complexity of neuron, the regulation and biogenesis of cytochrome c oxidase is also more complicated. In neurons, mitochondria are mainly localized in the axonal region. But for the cytochrome enzyme activation, mitochondria require nucleus encoded factors. Energy dependant microtubular transport is required for the transport of organelles inside neurons, which are also affected by defective mitochondria [89,99]. A recent review by Muller and co-workers, based on the *in vitro* and *in vivo* findings of AD models with regard to the mitochondrial function have analyzed the role of mitochondrial dysfunction in brain aging and AD [96]. Aβ toxicity in neurons is also promoted by the Aβ which target the mitochondria by stimulating the ROS generation and production of apoptogenic proteins [23,110]. Tau proteins are also reported to have similar ROS generating capacity by reducing the membrane potential of mitochondria [53]. The review by Colell et al. identifies mitochondrial cholesterol as a novel pathogenic factor in AD due to its mitochondrial glutathione (reduced) regulation favoring AD progression [23].

## 3. Cholesterol in Alzheimer's disease

### 3.1. Role of cholesterol in health and well-being

Cholesterol ($C_{27}H_{46}O$), an integral component of all animal cells is a versatile compound with a myriad array of functions in living systems [104,166]. The structure of cholesterol (Fig. 2) consists of a polar head, a rigid steroid ring structure and a non polar hydrocarbon tail. Although at times portrayed as tantamount to poison, cholesterol is an essential structural component of animal cells and it is a substrate for the synthesis of a variety of sterols including vitamins, bile acids and steroid hormones. It is a major factor which influences the membrane order, dynamics and cellular stability. Cholesterol has a regulatory function in many enzyme and recep-

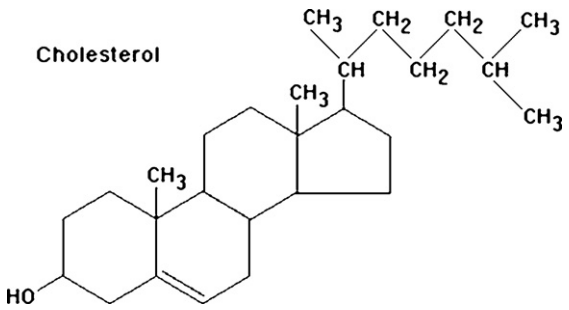


**Fig. 2.** Structure of cholesterol.

tor activities [30,83]. Due to these vital functions of cholesterol, the body requires a continuous supply of cholesterol which is mainly attained by the *in vivo* biosynthesis utilizing the HMG CoA pathway (Fig. 3) or through the diet [166].

No enzymes are capable of degrading the sterol ring of cholesterol and so the accumulation of cholesterol would be detrimental. The cholesterol is excreted from the body by two different means-excreted as cholesterol through the intestines or sloughing of the skin and by the conversion to bile acids or steroid hormones. To maintain the delicate balance of cholesterol in body, an intricate regulatory and transport mechanism has evolved to ensure proper cholesterol homeostasis [33]. The rate limiting step in the biosynthesis of cholesterol is the formation of mevalonate (Fig. 3), which is catalysed by 3-hydroxyl-3-methylglutaryl-CoA reductase (HMG-CoAR). This conversion is inhibited by statins (HMG-CoA reductase inhibitors). However, this may stop the synthesis of various downstream products with eminent metabolic functions, like the different isoprenoids and ubiquinone [3,97]. Although cholesterol is a vital entity for the normal functioning of the living system, an increase or any change in the concentration or homeostasis of cholesterol has serious discursive effect. It has been found to be a major factor contributing to various diseases including coronary heart disease, stroke, other vascular conditions and neurodegenerative diseases to name a few [27,68,117,127].

### 3.2. Cholesterol in brain

Brain is the most cholesterol rich organ in human body with approximately 25% of the total cholesterol in the body present in brain and several pathways are involved in the transport and storage of cholesterol in the central nervous system (CNS) [134]. In brain, cholesterol is localized in the specialized membranes of

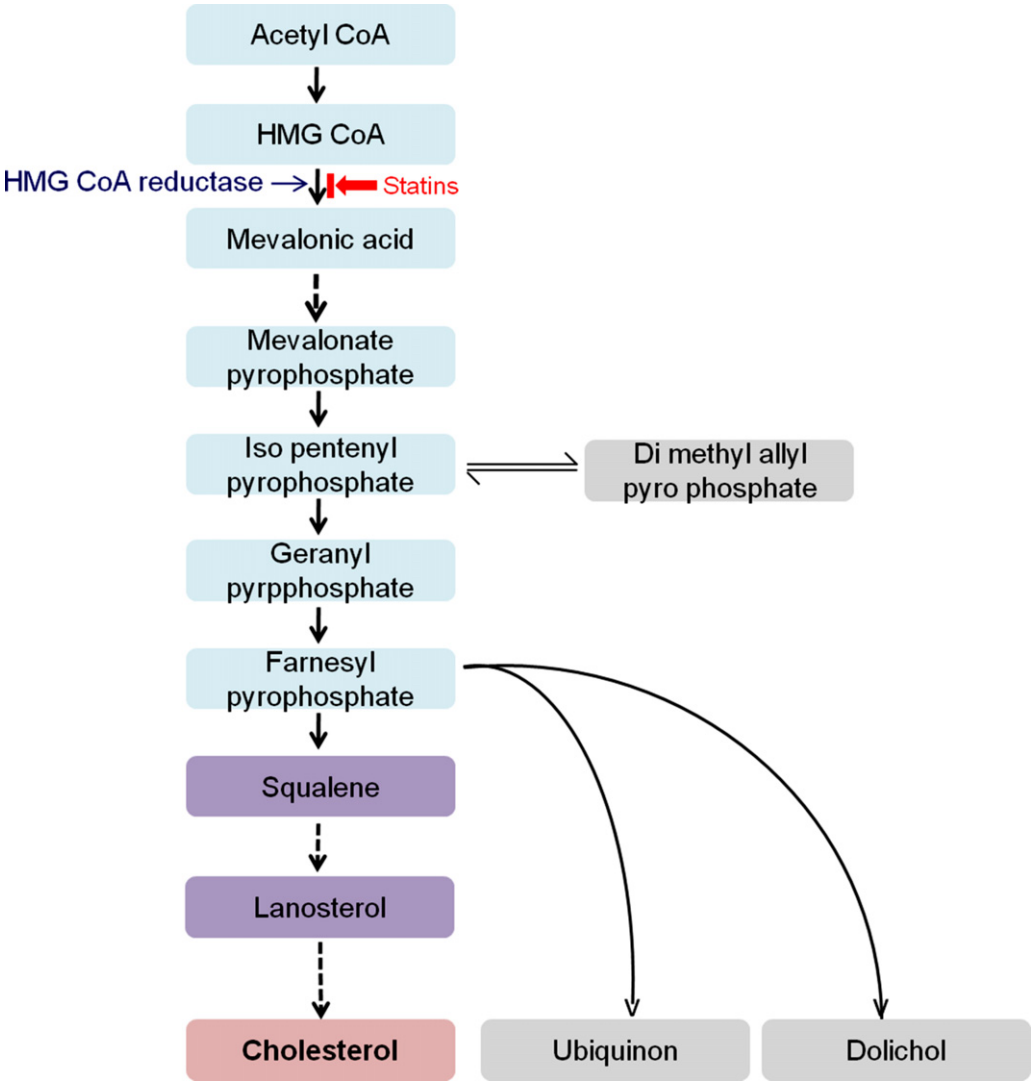


**Fig. 3.** A simplified representation of HMG-CoA pathway of *de novo* cholesterol biosynthesis in animal cells.

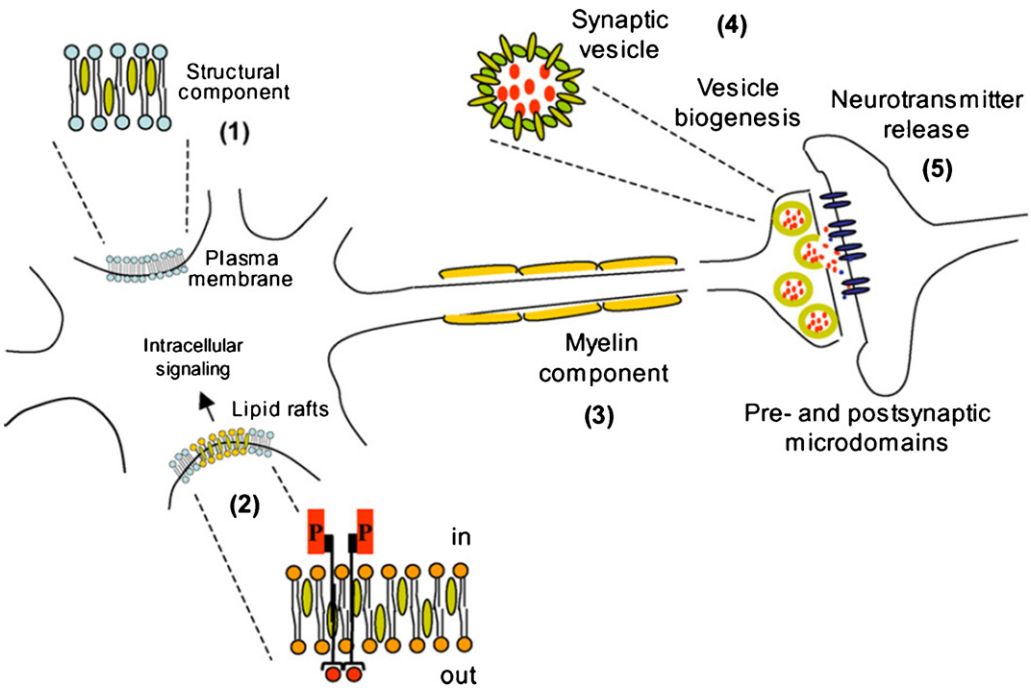


**Fig. 4.** A representation of the various roles played by cholesterol (green ovals) in different sites of CNS. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)
Adapted with permission from Valenza and Cattaneo [148].

myelin, neuronal and glial cells. The synthesis, efflux and influx of cholesterol in brain are highly regulated due to the presence of the BBB and various transporter proteins [52]. Cholesterol constitutes up to 25% of the membrane lipids in the nerve cells and is important for neuronal plasticity. It is required for the synthesis of neuronal synapses. Cholesterol plays a major role in the physiochemical properties of neural membranes and regulates the membrane bound enzymes, receptors and ion channels, along with endocytosis and antigen expression [30,38,83,104,148]. Fig. 4 depicts the various roles of cholesterol in CNS.

While there is mounting evidence on the negative impact of cholesterol on brain, it should not be forgotten that cholesterol is a protector of cholinergic processes. Iwo J. Bohr [10] through his hypothesis strongly criticizes the negative attitude towards cholesterol. Lipid rafts – the cholesterol and sphingolipid rich plasma membrane microdomains are integral in neuronal cell adhesion, axonal guidance and synaptic transmission. They are also crucial for the growth-factor signal transduction, vesicular trafficking and membrane associated proteolysis and help the neurons to compartmentalize and regulate these processes [10,147].

Glial cells and neurons can synthesize its own cholesterol via the HMG-CoA reductase pathway and is almost entirely independent of the plasma cholesterol. The cholesterol forms complexes with apolipoprotein E (ApoE) and phospholipids for delivery to neurons and for the formation of new membranes and synapses. ApoE is the most prevalent lipoprotein in the CNS and brain is the second major site of synthesis of ApoE [37]. Though brain is capable of *in situ* synthesis of cholesterol, it cannot degrade it and require expulsion of cholesterol in to the plasma for degradation and elimination. In the AD affected brain, there is an increase in the release of cholesterol due to the degenerating synapses and neurons and also due to the dysregulated ApoE transport. Excess cholesterol in brain is converted to 24-hydroxy cholesterol in the neurons. This is later transported via the ApoE, via the blood brain barrier into the plasma. It is then excreted into the bile from liver [9,134,162]. In brain, the highest rate of cholesterol synthesis occurs during the first postnatal weeks, which accounts for the requirement and utilization in glial cell proliferation, neurite outgrowth, microtubule stability, synaptogenesis and myelination. The high amount of cholesterol in the myelin sheath provides insulation to the axons and help in the easier conduction of action potentials [83].

### 3.3. Cholesterol in pathogenesis of Alzheimer's disease

From the studies of the past ten years, there has been mounting evidence suggesting that cholesterol plays an active role in the progression of AD. Many reviews and research reports have dissected the role of cholesterol in AD. The most important of these reports are by Simons et al. [135], Frears et al. [42], Hartmann [51], Refolo et al. [112], Fassbender et al. [39], Eckert et al. [35], Puglielli et al. [107,108] to highlight a few. It is the intracellular cholesterol distribution and homeostasis that is implicated rather than the total cholesterol levels in the development of AD [107,108,134]. In 2004, a review by Miller and Chacko selected and reviewed clinical studies based on AD, with special attention to use of statins [95]. Similar review was published by Sjogren et al. in 2006, consolidating the research results spanning a time period of ten years [136]. A review by Martin et al. (2010) has in depth discussed the changes in cerebral cholesterol during normal and pathological aging. Their review analyses the advantageous and disadvantageous roles of cholesterol in brain with relation to aging [88].

#### 3.3.1. Cholesterol in amyloid beta synthesis

Dysregulated lipid metabolism participates in the pathogenesis of neurodegenerative disorders [56,70]. One of the first reports on the role of membrane cholesterol in Alzheimer's was by Sparks et al. in 1994 [139]. Since then, many studies have tried to understand the role of cholesterol in Alzheimer's disease, but the results have been highly controversial. The activity of enzymes

involved in the APP metabolism is influenced by cholesterol. As the post transcriptional processing of APP occurs in cholesterol rich membrane domains, lower levels of cholesterol disrupt the membrane micro-domains and thus making the APP available for proteolysis by α-secretase. This has been validated in mice and guinea pigs, by increasing and decreasing the levels of cholesterol and studying the generation of amyloid beta fragments [39,111,134]. Changes in membrane properties like fluidity and stiffness has been suggested to influence the activities of membrane bound proteins and enzymes. It has been reported that the high cholesterol content in the lipid rafts facilitates the optimal configuration of the APP for the processing by β and γ secretases [153,161].

#### 3.3.2. Tau proteins and cholesterol

The role of cholesterol in the tau phosphorylation is still not clearly defined. Zou et al. in 2003 reported the increase in the tau hyperphosphorylation when Aβ42 was injected into the rat cortices [175]. Since cholesterol and amyloid fragments are related, this report has showed an indirect relation of cholesterol with tau proteins. Similar observation where tau phosphorylation and cholesterol are linked was reported by Koudinov and Koudinova [75] and Rahman and co-workers [109].

### 3.4. Cholesterol homeostasis in brain

Homeostatic mechanisms perturbed by genetic, environmental, natural aging, nutritional factors or mutations can lead to modified cellular activities, which in turn can terminate in diseased states. A series of interdependent processes including synthesis, storage, transport and removal is involved in the homeostasis of cholesterol in brain [134]. Cholesterol homeostasis in brain occur via different pathways involving the sterol regulator element binding proteins, transcription factors regulating cholesterol, fatty acid synthesis pathways and liver X receptors (LXRs). Of these Liver X receptors are the master regulators of cholesterol homeostasis in brain [18].

The major rate limiting step in the *de-novo* synthesis of cholesterol is the conversion of HMG CoA to Mevalonic acid by HMG CoA reductase enzyme (Fig. 3). ApoE is the predominant cholesterol carrier in CNS and ABCA1 regulates the secretion of ApoE from astrocytes and microglia. ABCA1 is the major cholesterol transporter across brain. The most important mechanism of elimination of cholesterol is by the conversion to 24S-hydroxy cholesterol by the CYP46 enzyme- cholesterol 24-hydroxylase. 24-S hydroxyl cholesterol is able to cross the BBB and get into the circulating plasma cholesterol pool [83,122].

Liver X receptors (LXRs) are ligand-activated transcription factors belonging to the nuclear hormone receptor family of transcription factors and are important regulators of cholesterol, fatty acid and glucose homeostasis [14,130,133,141,143]. LXR were first identified in 1994 and was categorized as orphan receptors. It occurs in two isoforms – LXR α and LXR β. LXR α is present in liver, kidney, fat tissue, macrophages, lungs and spleen, while LXR β is a ubiquitous receptor [6,140]. Apart from cholesterol and other fatty acid metabolism and transport, LXRs regulate carbohydrate metabolism, endocrine homeostasis and inflammation [19,65,118,140,146]. LXR nuclear receptors are activated by specific ligands, which bind to the LXR response elements on the promoter regions of genes under the control of LXR and release the corepressors, there by activating the transcription of these specific genes [6,141,160]. LXR activation leads to the increased transcription of cholesterol efflux proteins like apo E and transporters of ABC family, and metabolizing enzymes like the Cyp genes and stearoyl CoA desaturase. Former studies have shown that the ABC A1 expression has lead to the increased export of 24-hydroxy cholesterol to plasma and decreased production of amyloid beta by APP processing. Evidences from genetic studies have identified ApoE, the major carrier of cholesterol in the central nervous system to be the primary risk factor in sporadic AD [84,116,124].

Activation of LXR results not only in cholesterol elimination from the brain, but are involved in neuroprotective activities including the activation of sterol elimination pathway, apolipoprotein activation and regulation of APP processing [160]. Oxygenated derivatives of cholesterol called oxysterols are the natural endogenous ligands for LXR [140,146,160]. Few examples are 22(R)-hydroxy cholesterol, 24(S)-hydroxyl cholesterol, 27-hydroxyl cholesterol and cholestenoic acid. Intermediates of the cholesterol biosynthetic pathways also act as LXR ligands. Resveratrol, sigmasterol and sitosterol are plant derived LXR activators [14,60]. The first natural non-oxysterol ligand of LXR was reported by Bramlett et al. in 2003, from *Penicillium paxilli* called paxilline, and was found to be functional against LXRα and LXR β [14]. Few synthetic ligands (TO901317, T1317 and GW3965) have been synthesized and these also have shown to enhance LXR activating genes [32,156,169]. Koldamova et al. [71] and Riddell et al. [119] have reported the use of LXR agonist TO901317 for lowering the amyloid levels in mice models of AD.

Table 1 lists out various genes involved with the cholesterol homeostasis and metabolism, which are associated with AD.

### 3.5. Previous studies on AD–cholesterol relation

As mentioned earlier, hypercholesterolemia is non-genetic risk factor for the development of AD [17,69]. To analyze the effect of varying concentration of cholesterol on amyloid formation, cells incubated in lipid depleted serum were treated with various concentrations of statins and then subsequently tested for amyloid formation. The results of this study suggest that amyloid formation was reduced by reducing the cellular cholesterol, which might be either due to altered trafficking of amyloid fragments, or due to the modification in protease activity. The authors, Buxbaum et al., also suggest that reducing cholesterol levels may delay the onset or slow the progression of AD [17]. Similar suggestion was proposed by Borroni et al. with supporting evidence from their study evaluating the rate of decline in AD patients on choline esterase inhibitor treatment and the role of serum cholesterol on the effect of medication [12]. Yao and Papadopoulos used cholesterol–protein binding blot assay to study the Aβ-cholesterol interaction and found that cholesterol binds to the APP at the α-secretase cleavage site, favoring the β-secretase activity. Cholesterol binding to APP leads to the increased production of Aβ which competes with LDL-mediated cholesterol influx (decreased cellular cholesterol) which makes the authors to conclude that a major physiological role of Aβ and APP is in regulating cholesterol transport and homeostasis [164]. Cholesterol rich diet has shown to increase the accumulation of amyloid plaques in experiments with rabbits [138]. Similar action was also observed in APP transgenic mice, which showed increased cerebral amyloid deposition with cholesterol enriched diet [112,132]. Epidemiological studies on patients taking cholesterol-lowering statins have shown a lower prevalence of AD [63,121,167]. Statins reduce endogenous cholesterol synthesis and have numerous pleiotropic actions, such as the reduction in protein isoprenylation [113]. ApoE is the main transporter protein of cholesterol in brain and the mutations to ApoE has shown to increase the prevalence of early onset AD [52]. Molecular and mechanistic evidence from various studies point towards the role of cholesterol in AD: cholesterol enhancing the γ secretase-mediated synthesis of amyloid plaques and cholesteryl esters stimulate non-amyloidogenic APP degradation [52,107]. Avdulov et al. in 1997 found that Aβ aggregates shows inclination to bind with choles-

**Table 1**
Genes involved in lipid metabolism associated with late onset AD.

| Gene | Potential functions in AD | Reference |
|---|---|---|
| APO genes | Peripheral and CNS cholesterol transport, Aβ disposition and clearance | Martin et al., 2000 [87]; Takei et al., 2009 [142] |
| A2M | ApoE binding, Aβ clearance | Borth, 1992 [13]; Korovaitseva et al., 1999 [73]; Kovacs, 2000 [78] |
| LRP1 | ApoE binding, Aβ clearance | Donahue et al., 2006 [34]; Harris-White and Frautschy, 2005 [50] |
| IDE | Aβ degradation | Bjork et al., 2007 [8]; Edland et al., 2003 [36]; Sato et al., 2008 [128] |
| ABC family of genes | Regulation of intracellular cholesterol levels, lipid transport in periphery and CNS, Aβ formation, deposition and clearance | Rodriguez-Rodriguez et al., 2009 [122]; Shibata et al., 2006 [131]; Wang and Jia, 2007 [155]; Wavrant-De Vriese, 2007 [157] |
| ACAT/SOAT | Regulation of intracellular cholesterol levels, Aβ formation | Huttunen and Kovacs, 2008 [59]; Puglielli et al., 2004 [105] |
| CH25H | Regulation of intracellular cholesterol homeostasis | Papassotiropoulos et al., 2005 [100]; Riemenschneider et al., 2004 [120]; Shibata et al., 2006 [131] |
| CYP46 | Regulation of CNS cholesterol turnover | Borroni et al., 2004 [11]; Combarros et al., 2004 [24]; Corbo et al., 2009 [25]; Papassotiropoulos et al., 2003 [101]; Wang and Jia, 2007 [155] |

terol [5]. Cutler et al. and Wood et al. have reported the increase in brain cholesterol levels during AD progression [29,163].

Brain homogenates from transgenic mice expressing human APP751 with the Swedish mutation under murine Thy1 promoter, fed on plant sterols and cholesterol were analyzed for sterol profile. Groups of five wild type and five APP-transgenic mice at 3, 6, 9 and 12 months and 10 wild type and 11 APP transgenic mice at 18 months were the subjects of the study. They found that cholesterol was synthesized utilizing two different pathways – desmosterol pathway in young brain and lathosterol pathway in aged brain. Plant sterol fed APP transgenic mice showed higher campesterol and sitosterol levels suggesting impairment in the stringency of BBB [85]. Studies done by Puglielli and Kovacs and their co-workers [105] based on their studies on acyl coenzyme A transferase (ACAT), reports that reduction in hypercholesterolemia and brain cholesterol by statins is a potential strategy to reduce amyloid accumulation in AD. ACAT plays a pivotal role in the regulation, distribution and homeostasis of cholesterol in all tissue types of the body. Inhibition of ACAT can lower the cholesterol absorption in tissues, and this can indirectly reduce the amyloid production. In another report, Puglielli and co-workers demonstrated that Aβ mimics the activity of cholesterol oxidase, both *in vitro* and *in vivo*. They reported that highly redox-reactive Aβ:$Cu^{2+}$ complex resemble and replicate mammalian cholesterol oxidase activity in catalytically generating neurotoxic $H_2O_2$ by the reduction of $Cu^{2+}$, which corresponds with the initiation of apoptotic pathway and cellular toxicity. The authors suggest that use of statins to inhibit cholesterol production and drugs which inhibit Aβ cholesterol oxidase activity have the potentials to be powerful drugs in AD [106].

To study the role of cholesterol in synaptic plasticity, hippocampal slices of naïve albino Wistar rats were used by Koudinov and Koudinova [77]. They have reported that cholesterol is an essential factor in maintaining synaptic plasticity, the failure of which causes various neuronal changes. The authors suggest that alterations in the cholesterol homeostasis are the primary unifying cause of various neurodegenerative diseases. In a study done on New Zealand white female rabbits, it was observed that brain cholesterol levels were not affected by increased dietary cholesterol, but cellular cholesterol of neurons showed significant higher levels, while neurons from controls showed no marked variation. Increase in BACE activity and Aβ1–42 like-plaques were also observed in the hippocampus of the cholesterol-fed rabbits, while tau hyperphosphorylation was not observed [43]. A study on sporadic inclusion body myositis (IBM) done using rabbits fed on cholesterol-enriched diet reported increased APP expression and Aβ production in skeletal muscles [22]. In a study conducted in Swiss-Webster mice, statin (simvastatin, lovastatin and atorvastatin) administration was reported to reduce amyloid β formation both under *in vitro* and *in vivo* conditions. The study by Burns et al. reports that cholesterol distribution in the plasma membrane is more important than the total level [16]. Another study with New Zealand white male rabbits fed with 2% (w:w) cholesterol found similar results, reporting significantly increased levels of Aβ in the cortex of the cholesterol-fed rabbits, when compared to control rabbits. Confocal microscopy of hippocampus and cortex showed increased BACE1 and RAGE levels, while IDE and LRP-1 showed decreased levels in association with increased Aβ levels of cholesterol fed rabbits [61].

In a Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) study aimed to examine the association of statin use before the onset of AD and the impact of ApoE genotype, it was concluded that statin medication proved beneficial in the specific study population and lowered AD incidence [46]. Interaction of Aβ and cholesterol was further analyzed using transmission electron microscopy (TEM) by negatively staining the specimen. Binding characteristics were analyzed in preformed amyloid β (1–42) fibrils and during fibrillation process. It is supposed that cholesterol binds to the Aβ 17–21 hydrophobic cholesterol binding motif on the fibrillar structures and the availability of this region is different in preformed fibrils and during the fibrillation process, resulting in different patterns of cholesterol binding [49]. Altered brain cholesterol metabolism with relation to development and progression of AD was studied by Halford and Russel in wild type (WT), 24-hydroxylase knockout (KO) and WT and KO mice expressing AD transgenes (WT/AD and (KO/AD). The study concluded that there was no significant decrease in the amyloid plaque formation in the cortex and hippocampus of the mice by decreasing the *de novo* cholesterol synthesis by genetic means. Interestingly, it was observed that the decrease in cholesterol synthesis by the loss of hydroxylase genes helped in prolonging the life of AD mice of both sexes. They have also reported similar profile for secretase activity the WT/AD and KO/AD mice, implying normal cholesterol metabolism in KO mice [48]. Although there are conflicting reports on the efficacy of statins against neurodegenerative diseases, a large percentage of studies summarize that statins seem to invoke a general neuroprotective mechanism in different neuropathogenic conditions. Most and co-workers have published a review discussing the probable mechanism of neuroprotection by statins. In their review, van der Most et al. suggest that, even though most of the statins are incapable of crossing the BBB, peripheral effects like the reduction of oxidative damage, improvement of vascular function and modulation of peripheral inflammatory response help in overcoming the neurological defects [151]. The mechanism of the effects of statins in brain is not yet clearly understood and they might not be the exact cure for AD, but none the less, their role in the reduction of peripheral cholesterol and anti-inflammatory property might play a role in the increased cerebral oxygenation, which in turn is beneficial for brain functioning [88].

As mentioned earlier, cholesterol has various beneficial roles to play in the brain. Apart from the previous reports of negative role of cholesterol in brain, many other literatures have suggested a protective role of cholesterol in brain, suggesting that depleted brain cholesterol favors neurodegeneration. Protective effects of cholesterol against neurotoxic amyloid fragments were reported by Zhou and Richardson [171] and Yip et al. [165]. Mason and co-workers reported that they found the neuronal cells of Alzheimer patients to be cholesterol drained [90]. Cholesterol has shown to inhibit the channel formation on the lipid bilayer by the amyloid fragments [82]. Tau protein accumulation, another hallmark of Alzheimer's, has been shown to be favored by cholesterol depletion [76]. Structural study of neuronal diffraction conducted by Dante et al. reports that cholesterol inhibits the insertion of monomeric amyloid fragments into the lipid membrane and this supports the protective effect of cholesterol [30]. It was reported that higher concentrations of lovastatin suppressing cholesterol and its precursor geranylgeranlypyrophosphate formation, resulted in the tau hyperphosphorylation and apoptosis [94]. In another study, lovastatin was administered to transgenic mice – Tg2576 and was observed that lovastatin enhanced the β-secretase activity and enhanced amyloid production selectively in female mice. Although the lovastatin reduced the plasma cholesterol levels in both male and female mice, only female mice showed enhanced amyloid deposition. The results from this study suggest that sex dependant differences exist in problems due to lower brain cholesterol [102]. Abad-Rodriguez and co-workers studied the neuronal membrane dynamics in AD and their study concluded that lower levels of CNS cholesterol affect the neuronal function negatively [1]. An important paper worth mentioning is by Crameri et al. [26], where they have discussed the role of seladin-1, the cholesterol-synthesizing enzyme, in neuroprotection. Seladin-1 is downregulated in affected neurons of AD and is suggested that seladin-1-dependant cholesterol synthesis is involved in lowering the amyloid levels of AD. They have reported that enhancing seladin-1 activity might be advantageous in AD therapy. The results of a large-scale randomized study by Feldman et al. reports that statin therapy (atorvastatin) in mild to moderate cases of AD did not produce any significant clinical benefits with over 72 weeks of treatment. This is the first reported large scale, randomized control trail analyzing the Lipitor's Effect in Alzheimer's Dementia (LEADe). They also report that the atorvastatin treatment was well tolerated and did not produce any unexpected adverse reactions. This study was also beneficial in providing safety and dosage information on atorvastatin usage in elderly population with AD [40]. Similar result was published by Fillit in mild to moderate cases of AD on donepexil with atorvastatin [41]. A recent study conducted by Kolsch et al. analyzed the variation in levels of cholesterol and its precursors – lanosterol, lanthosterol and desmosterol in the cerebrospinal fluid and plasma of AD patients and compared it to that of non-demented controls. The results from the study suggest that there is a disturbance in the *de novo* synthesis of cholesterol of AD patients, resulting in lower levels of cerebral cholesterol. The authors suggest that this lowered level of cholesterol may affect neuronal regeneration in the brain and may worsen the cognitive functions [72].

## 4. Cholesterol in other neurodegenerative diseases

Apart from being the structural component of myelin and plasma, cholesterol in brain has various cellular functions like membrane trafficking, signal transduction, myelin formation and synaptogenesis. Neurodegenerative diseases result from the deterioration of neurons or their myelin sheaths, which eventually leads to neuronal death and there by CNS-related dysfunction. Cells of the brain and spinal cord do not regenerate *en masse*, therefore excessive damage can be disastrous. Due to this, cholesterol homeostasis in the brain is a vital affair [83,148].

Niemann–Pick disease is a fatal, inherited error of lipid metabolism, with autosomal pattern of inheritance. The breakdown, transport and the use of fats and cholesterol in the body is affected and results in the accumulation of harmful amounts of lipids in spleen, liver, lungs, bone marrow and brain [103]. Niemann–Pick Type C disease (NPC) is a sub-acute progressive neurodegenerative disorder due to erroneous cholesterol trafficking resulting in the cholesterol and sphingolipid accumulation in endosomes and lysosomes of neurons [83]. Improper neuronal cholesterol homeostasis might be an underlying cause for the synaptic degeneration and formation of neurofibrillary tangles in Niemann–Pick disease [77].

Parkinson's disease (PD) is the second most common neurodegenerative disease manifested by bradykinesia, resting tremor, muscular rigidity, gait disturbances, and postural reflex impairment. The studies on the association between serum total cholesterol and the risk of PD are few and the results are inconsistent. A prospective study in Finland showed that high total cholesterol at baseline is associated with an increased risk of PD, while higher serum levels of total cholesterol has been found to be a protective factor in an earlier study. The exact molecular mechanism of cholesterol in PD is not yet elucidated and more studies are necessary for a conclusion [58,83].

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by behavioral abnormalities, cognitive decline, and involuntary movements that lead to a progressive decline in functional capacity, independence, and ultimately death [150]. Recent studies have shown that cholesterol metabolism is disrupted in Huntington's disease. The lipid dysregulation has been linked to the mutant huntingtin protein on the sterol regulatory element proteins, resulting in lower cholesterol levels in the HD affected parts of the brain [148,149].

Apart from these well known diseases, cholesterol synthesis is also seen in association with Smith-Lemi Opitz Syndrome (SLOS), an autosomal recessive syndrome manifested by distorted facial features, developmental delay, mental retardation, microcephaly and hypospadias. In SLOS, 7-dehydroxy cholesterol reductase, the final enzyme in cholesterol biosynthesis pathway is inactivated, thus resulting in an inefficient cholesterol synthesis and accumulation of 7-dehydroxy cholesterol [148].

## 5. Conclusion and future directions

Alzheimer's disease is a menacing debilitating disease, to which no one is immune. Although multiple drugs have now been approved, their benefits are symptomatic and modest. Moreover, AD being multifactorial in origin, synergistic efforts to regulate multiple mechanisms are the need of the hour for efficient control of the disease. Various factors, however seemingly inconsequential, which contribute to this affliction has to be studied thoroughly in great detail. Defective cholesterol metabolism and hypercholesterolemia plays a villainous role in many disease states including neurodegenerative diseases. There is no doubt regarding the necessity of cholesterol in proper functioning of the brain, however cholesterol homeostasis is deregulated in aging brain which affects the normal activities in the brain. Although not very clear, brain and the peripheral cholesterol levels are intricately linked, making the reduction of peripheral cholesterol influence the cholesterol homeostasis in brain. Though this may not be equally beneficial to everyone, it seems to be significant in persons with hypercholesterolemia and high dietary cholesterol intake. Moreover, statins in general have anti-inflammatory property too, which is indeed useful in the case of AD. Along with other factors like

oxidative stress and dysfunctional mitochondria, aberrant levels of cholesterol might prove to be detrimental to the brain and its functions. The equivocal results obtained in favor and against the role of cholesterol might be dependent on various study parameters like pharmacology and blood–brain barrier permeability of statins, sex and neuropathology of the animal models and timing of the exposure of the drug. Although the statins decrease the plasma cholesterol levels, there is no finite answer on the activity of the statins on the brain cholesterol and its end effect. A number of questions still remain unanswered with respect to the role of cholesterol in aging and disease states. Mechanisms which control the regulation of cholesterol metabolism is a factor that has to be looked into with more diligence, particularly with respect to neurodegenerative diseases like AD. It is hoped that drugs modifying the cholesterol metabolism or molecules which modulate the membrane properties can be utilized as a successful therapeutic approach or for the prevention of Alzheimer's disease. Humble initiatives of preventive strategies which can delay the onset and progression of Alzheimer's can significantly reduce the extensive global burden of the disease. Promising theoretical and experimental data has to be translated into clinical trials and assessed prudently for swifter advancement in therapeutic materialization.

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