Chapter 13
Nanolipidic Carriers as Potential Drug Delivery Vehicles in Alzheimer's Disease

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Abstract Alzheimer's disease (AD) is the most common cause of dementia accounting for about 60–80% of the cases. With the rise of population of elderly people all over the world, providing greater medical relief to the patients suffering from Alzheimer's disease has become a matter of great urgency. The exact etiology of AD is still unexplained but several hypotheses explaining the pathophysiology of AD have been put forward.

The currently approved pharmacotherapy of AD utilizes cholinesterase inhibitors and NMDA receptor antagonists which provide only symptomatic relief. The drugs used for treatment of Alzheimer's disease should be able to cross the blood-brain barrier (BBB) and reach the central nervous system before the therapeutic effect can be exerted. Therefore, it is a big challenge to design drug delivery system (DDS) capable of targeting drugs to the intended delivery site in the brain.

Lipid-based nanosized drug delivery systems seem to be very promising in delivering the entrapped drug to the brain by virtue of their lipidic nature and small size. Lipid-based nanocarriers have the added advantage of very low cytotoxicity and avoidance of P-glycoprotein-mediated efflux activity of brain endothelial cells apart from other advantages like ability to entrap both hydrophobic and hydrophilic drugs and greater entrapment efficacy. The aim of the present chapter to review the treatment options currently available for Alzheimer's disease and various lipid-based nanocarrier systems explored for enhancing the therapeutic efficacy of anti-Alzheimer drugs along with the challenges in targeting delivery of drugs to the brain.

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13.1 Introduction

With increasing lifespan of people and increasing aging populations around the world, the concerns associated with quality of life also continue to increase. One of the leading causes of compromised quality of life in the geriatric population is Alzheimer's disease (Prince and Jackson 2009). AD is a neurodegenerative disorder characterized by a progressive and irreversible neuronal damage that was described for the first time by the German Physician Alois Alzheimer in the year 1906 (Stelzmann et al. 1995). Accounting for 60–70% of cases of dementia, AD is the leading cause of dementia worldwide (www.who.int). Based on epidemiological data collected in recent years, Alzheimer's Disease International (ADI) estimated incidence of AD in 14th World Health Organization (WHO) regions in 2005. The results showed that North America and Western Europe have the highest prevalence of dementia (6.4 and 5.4% of the population at age 60), followed by Latin America (4.9%) and China and its developing Western Pacific neighbors (4.0%). Compared with Africa, Asia, and Europe, the prevalence of AD was higher in the USA (Ferri et al. 2005).

The nine countries with the largest number of people with dementia in 2010 were China (5.4 million), USA (3.9 million), India (3.7 million), Japan (2.5 million), Germany (1.5 million), Russia (1.2 million), France (1.1 million), Italy (1.1 million), and Brazil (1.0 million).

According to WHO, there were 50 million registered cases of dementia in 2017. Every year, there are nearly 10 million new cases. The total number of people with dementia is expected to reach 82 million in 2030 and 152 million in 2050 globally (www.who.int). Though 1–6% of the AD cases emerge in people aged between 30 and 60 years, which is known as early-onset AD, in 90% cases, AD occurs in people older than 60 years (Mullane and Williams 2013).

Every 65 s someone in USA develops AD (Alzheimer's Association 2018). AD is the 6th leading cause of death in the USA. One in three senior dies with AD in the USA. 16.1 million Americans provide unpaid care to people with AD or other dementias. An estimated 5.7 million Americans of all ages are living with Alzheimer's dementia in 2018. This number includes an estimated 5.5 million people age 65 and older and approximately 200,000 individuals under age 65 who have younger-onset Alzheimer's, though there is uncertainty about the younger-onset estimate (Alzheimer's Association 2006) (Hebert et al. 2013). In the USA, the percentage of people with Alzheimer's dementia increases with age: 3% of people age 65–74, 17% of people age 75–84, and 32% of people age 85 and older have Alzheimer's dementia (Hebert et al. 2013).

Dementia which is a characteristic symptom of AD causes disability and dependency in patients all over the world. It is caused by an abnormal aging of the central nervous system (CNS) with decrease in cognitive function, memory, thinking ability, reasoning, and learning (Ferretti et al. 2018). Dementia severely impacts the work and social life of the persons as the affected persons find it difficult to express themselves. With the progression of the disease, the patients require extensive help with their daily activities as well (Alzheimer's Association 2012).

According to the WHO report 2008, treating and caring for people with dementia costs the world more than US$ 604 billion per year (World Health Organization 2008). This includes the cost of providing health and social care as well as the reduction or loss of income of people with dementia and their caregivers. In Europe it is estimated that the future cost of dementia would rise by approximately 43% from 2008 reaching 250 billion Euros in 2030.

The aim of the present chapter is to provide a brief overview of AD with underlying pathophysiology and the currently available treatment modalities. The chapter also reviews in detail the potential role that lipid-based nanocarriers can play in increasing the efficacy of the anti-Alzheimer drugs by selectively delivering these to the central nervous system (CNS).

13.1.1 Stages of Alzheimer's Disease

The stages are separated into three categories: mild Alzheimer's disease (early stage), moderate Alzheimer's disease (middle stage), and severe Alzheimer's disease (late stage). The pace at which symptoms advance from mild to moderate to severe varies from person to person (Fig. 13.1). On average, a person with Alzheimer's has lifespan of 4–8 years after diagnosis, but he can live as long as

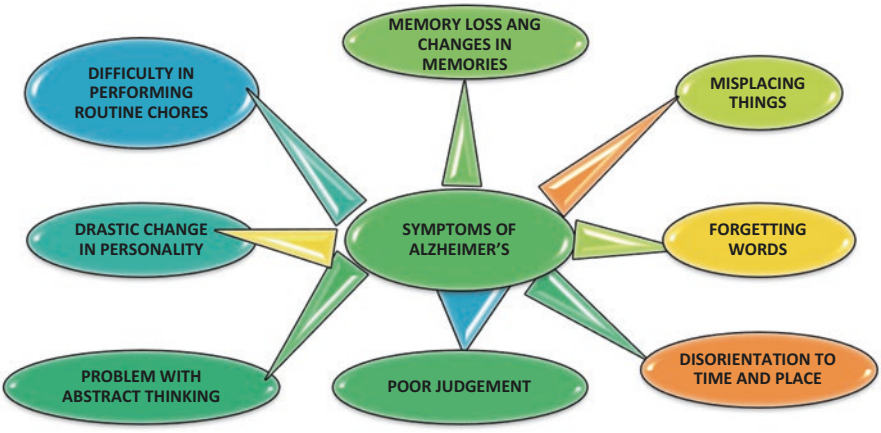

Fig. 13.1 Symptoms of Alzheimer's disease

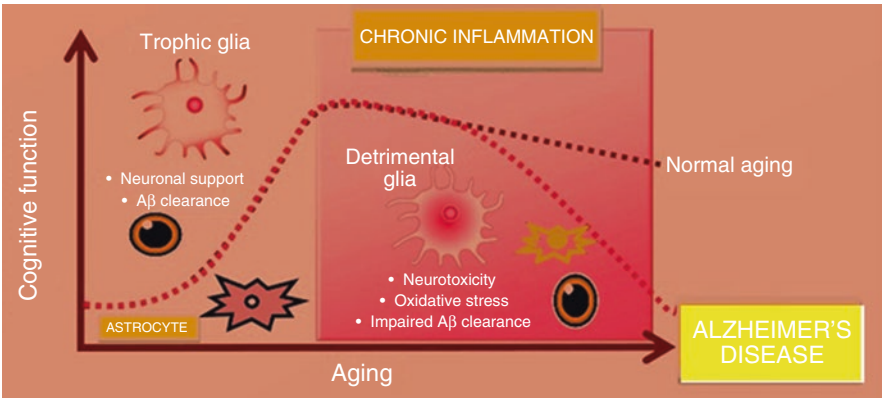

Fig. 13.2 Cognitive function with progression of Alzheimer's disease

20 years as well. Despite the categorization, practically it is difficult to put a person with Alzheimer's in a specific stage as stages may overlap. Figure 13.1 illustrates the different symptoms of AD and the decline in cognitive function in persons with AD vis-à-vis normal aging is illustrated in Fig. 13.2.

Mild Alzheimer's Disease (Early Stage)
The early stage is often mistaken. Relatives and friends (and sometimes professionals as well) confuse it with "old age." Because the onset of the disease is gradual, it is difficult to be sure exactly when it begins. Although the early stage patients can function independently, they may have difficulties like problems in having communication, i.e., difficulty in coming up with the right word or name; forgetfulness in remembrance of names when introduced to new people; impaired retention of content once read, heard, visualized, or written; lost abilities of planning or organization; and loss of track of the time, including day, month, year, etc.

Moderate Alzheimer's Disease (Middle Stage)
Moderate Alzheimer's is typically the longest stage and can last for many years. In this stage, the dementia symptoms are more noticeable to others and include: forgetfulness of events and one's own personal history, erratic mood and behavior, no interest in activities and hobbies, severe mood swings including depression or anxiety, and unable to recall their own address or telephone number and high school or college from which they graduated. Some patients feel trouble in controlling bladder and bowels also. Behavioral change like wandering, repeated questioning, calling out, clinging, disturbed sleeping, and hallucinations (seeing or hearing things which are not there) increases. Sleep pattern (circadian cycle) is lost and there are also chances of wandering and becoming lost. The patients also may require help at this stage for their personal care (i.e., toileting, washing, and dressing).

Severe Alzheimer's Disease (Late Stage)
In the final stage of this disease, dementia symptoms are severe. Individuals lose the ability to carry on a conversation and, eventually, to control movement. They may

still say words or phrases, but communicating becomes difficult. As memory and cognitive skills continue to worsen, significant personality changes may take place and individuals need extensive help with daily activities. At this stage, individuals may:

- need round-the-clock assistance with daily activities and personal care such as bathing and toileting
- lose awareness of recent experiences as well as of their surroundings
- experience changes in physical abilities, including the ability to walk (may be unable to walk or be confined to a wheelchair or bed), sit, and, eventually, swallow
- become vulnerable to infections, especially pneumonia
- be usually unaware of time and place
- have difficulty understanding what is happening around them
- be unable to recognize relatives, friends, and familiar objects
- have bladder and bowel incontinence
- have behavioral changes which may escalate and include aggression and nonverbal agitation (kicking, hitting, screaming, or moaning)
- be unable to find his or her way around the home

13.1.2 Risk Factors for Alzheimer's Disease

Experts believe that just like other diseases Alzheimer's develops as a result of multiple factors rather than a single cause. Some risk factors are discussed here.

Age—The percentage of people with Alzheimer's dementia increases dramatically with age: 3% of people aged 65–74, 17% of people aged 75–84, and 32% of people age 85 or older have Alzheimer's dementia (Hebert et al. 2013) but that does not imply that if a person is older he will develop Alzheimer's dementia (Fig. 13.2).

Family History—Individuals having parents or siblings with Alzheimer's are more likely to develop AD than those who do not have a first-degree relative with AD (Green et al. 2002).

APOE-e4 Gene—Everyone inherits one of three forms of the APOE gene: ε2, ε3, and ε4 from each parent. Having the ε4 form increases the risk of developing Alzheimer's Disease (Mahley and Rall 2000) and is more likely to develop Alzheimer's at a younger age (Spinney 2014).

Familial/Early Onset—Familial Alzheimer's Disease which develops before age 60 is due to mutations in the amyloid precursor protein (APP) and/or presenilin 1 and 2 gene (PSEN1 and PSEN 2).

Cerebrovascular Disease—According to Pendlebury and Rothwell (2009), there is twofold increased risk of dementia after first incident stroke. The mechanisms were believed to be destruction of brain parenchyma with atrophy, an increase in Aβ deposition, and the combination of vascular and Alzheimer-type pathology (Blennow et al. 2006).

Hypertension—Not only high but abnormally low blood pressure is also associated with dementia (Waldstein et al. 2005). In clinical trials, AD patients were given antihypertensive medications but the results were inconsistent (Lithell et al. 2003).

Type II Diabetes—Type II diabetes increases the risk of AD by twofold (Luchsinger et al. 2004). Reger et al. (2008) showed that the administration of intranasal insulin improved cognition in the patients who were in the early phases of AD. Same results were reported in a 6-month trial of the PPAR-g agonist, rosiglitazone, by Watson et al. (2005).

Smoking—Smoking either increases the risk of AD or there is no association (Doll et al. 2000). Nicotine increases acetylcholine release, elevates the number of nicotinic receptors, and improves attention but it also increases oxidative stress which contributes to AD (Rottkamp et al. 2000; Koponen et al. 2004).

Traumatic Brain Injury—Individuals having suffered traumatic brain injury have a higher risk of dementia, particularly those who carry the APOE-e4 allele (Koponen et al. 2004). Postmortem and experimental studies show that after human brain injury, both Aβ deposition (Hartman et al. 2002) and intraneuronal tau pathology are increased, even in younger patients (Smith et al. 2003). Higher levels of education, physical activity, and Mediterranean diet on the other hand were shown to decrease the risk of developing AD.

13.1.3 Diagnosis of Alzheimer's Disease

The revised guidelines of the National Institute on Aging (NIA) and the Alzheimer's Association (2012) incorporate some biomarker tests. A biomarker is a measurable indicator for the presence or absence of a disease or the risk of developing a disease. For example, blood glucose level is a biomarker of diabetes, and high blood pressure is a biomarker of heart disease risk. Some biomarkers for Alzheimer's are the amount of beta-amyloid in the brain as shown on positron emission tomography (PET) imaging, levels of certain proteins in fluid (e.g., levels of β-amyloid and tau in the cerebrospinal fluid and levels of particular groups of proteins in blood), and level of glucose metabolism in the brain as shown on PET imaging using the radiotracer fluorodeoxyglucose (Hyman et al. 2012).

13.1.4 Preclinical Alzheimer's Disease

In 1984 it was thought that AD begins when symptoms of dementia such as memory loss are already present and individuals fail to carry out daily tasks but due to revised guidelines it came to light that preclinical Alzheimer's disease is silent stage of AD in which individuals have no symptoms of memory loss but have measurable changes in the brain, cerebrospinal fluid, and/or blood (biomarkers) that indicate the earliest signs of disease showing that brain changes in

AD may begin 20 years or more before symptoms occur (Reiman et al. 2012; Bateman et al. 2012; Villemagne et al. 2013).

13.1.5 Mild Cognitive Impairment (MCI): A Potential Precursor to Alzheimer's and Other Dementias

MCI affects 15–20% of people age 65. In this condition, mild but measurable changes in thinking abilities can be easily noticed by the family members and friends of the person affected (Roberts and Knopman 2013). People with MCI are more likely to develop Alzheimer's than people without MCI (Kantarci et al. 2009). Revised guidelines suggest that if a person has MCI symptoms along with elevated levels of beta-amyloid, the individual may be in an early stage of Alzheimer's (called MCI due to Alzheimer's disease) (Sperling et al. 2011; Albert et al. 2011). However, MCI can develop for reasons other than Alzheimer's, and MCI does not always lead to dementia. In some individuals, MCI reverts to normal cognition or remains stable.

13.2 Etiology of Alzheimer's Disease

Though the cause of AD is still not fully understood, the complexity of AD pathophysiology has led researchers to propose several hypotheses that might contribute to the genesis of this disease. The most popular among these are the amyloid hypothesis and the tau hypothesis.

13.2.1 The Amyloid Hypothesis

The amyloid beta (Aβ) hypothesis is most widely accepted to explain the pathophysiology of AD. It states that Aβ deposition is the main and important causative factor of AD. Aβ is generated by the proteolysis of amyloid precursor protein (APP) which is a type I single-pass transmembrane protein expressed at high levels in the central nervous system (CNS). Though the exact physiological function of APP is not known, it is suggested to have a role in signaling pathways in the brain which includes synapse formation, neurogenesis, axonal transport, cell signaling, and plasticity (Thinakaran and Koo 2008). APP undergoes sequential proteolysis. It is first cleaved by α-secretase (nonamyloidogenic pathway) or β-secretase (BACE1) (amyloidogenic pathway) and then by γ-secretase (Vassar 2004). Non-amyloidogenic pathway is basically nontoxic and it starts by the cleavage of APP by α-secretase which generates a soluble sAPPα and a membrane-anchored C-terminal fragment C83. The C-terminal fragment (C83) is further cleaved by a γ-secretase to produce

a short fragment P3 and an APP intracellular domain (AICD). For the amyloidogenic pathway, APP is cleaved by β-secretase to produce sAPPβ and a C-terminal fragment containing 99 amino acids (C99). C99 is further cleaved by γ-secretase to form Aβ40 or Aβ42 fragment (Sahni 2011). Aβ peptide also has a tendency to form oligomers. Oligomers can form Aβ fibrils and protofibrils that will eventually form amyloid plaques preferably in the cerebral cortex and the hippocampus area of the brain (Golde 2005). These plaques activate microglial cells and astrocytes which trigger the release of inflammatory cytokines and chemokines leading to neuroinflammation and neuronal damage (Dzamba et al. 2016). Amyloid oligomers cause neurotoxicity and initiate the amyloid cascade. The elements of the cascade include local inflammation, oxidation, excitotoxicity (excessive glutamate), and tau hyperphosphorylation which ultimately results in cell death (Golde 2005). Healthy individuals do not have amyloid-induced cytotoxicity because of the fact that they can clear amyloid from the brain before it reaches neurotoxic levels by balancing amyloid production with its clearance (Hardy and Selkoe 2002).

It also needs to be mentioned that there are certain mutations in the presenilin 1 (PS1) and presenilin 2 (PS2) genes which account for most of the cases of familial early-onset AD (FAD) occurring in 30–50-year-old patients. The mutations in PS1 and PS2 increase the activity of γ-secretases. Because of increased γ-secretase activity, proteolysis of APP is also increased leading to enhanced Aβ formation, which is a characteristic of AD (Gopal 1999).

13.2.2 Tau Protein

Phosphorylated tau proteins are not causative factor for the disease but the reflection of neuro-damage (Hardy and Selkoe 2002). The inflammation produced by Aβ accumulation would lead to hyperphosphorylation of the microtubule-associated protein tau (De Paula et al. 2009). Tau protein is a microtubule-associated protein (MAP), which binds to the microtubules and stabilizes them (Weingarten et al. 1975). In the brain of AD patients, hyperphosphorylation of tau protein is at least three times higher than that in the normal brain (De Paula et al. 2009). This abnormal hyperphosphorylation causes the tau protein molecules to move away from the microtubules and misfold to stick to each other, ultimately forming paired helical filament (PHF) tau and neurofibrillary tangles (NFTs) (Gong and Iqbal 2008). NFTs negatively affect neurotransmitter transport and axonal integrity. This may ultimately lead to neurodegeneration in AD patients.

13.2.3 Cholinergic-Deficit Hypothesis

Rossor et al. (1980) and Henke and Lang (1983) reported that the brains of AD patients showed not only degeneration of cholinergic neurons but also reduction in cholinergic markers such as choline acetyltransferase (ChAT), the enzyme respon-

sible for the synthesis of acetylcholine (ACh). This led to the so-called cholinergic-deficit hypothesis of AD. Moreover, phospholipase A2 (PA2) enzyme which is responsible for the conversion of phosphatidylcholine to choline (Gattaz et al. 2014) has been reported to decrease in the frontal and parietal cortexes of AD patients and because choline is converted to acetylcholine by ChAT and AChE, its deficiency leads to cholinergic deficiency and AD progression. A study by Soininen et al. (1995) also showed that those AD patients which have the apolipoprotein E (APOE) ε4 allele have a more severe cholinergic deficit than the AD patients without the APOE ε4 allele.

13.2.4 Glial Cell Involvement in AD Pathophysiology

Glial cell-mediated inflammation plays an important role in AD pathophysiology. Four groups of glial cells are believed to be involved in AD pathophysiology: microglial cells, oligodendrocytes, NG2 glial cells, and astrocytes (Morales et al. 2014). Amyloid plaques or senile plaques activate microglial cells in their proximity which when activated performs the phagocytosis of cell debris or foreign particles and cytokines to protect CNS (Fu et al. 2014). Oligodendrocytes or oligodendroglia are a type of neuroglia whose main functions are to provide support and insulation to axons in the central nervous system by providing myelin sheaths which allow the fast propagation of action potentials, but when oligodendrocytes are in the vicinity of the amyloid or senile plaques, they release iron contained inside them. Iron is directly involved in myelin production and its deficiency in oligodendrocytes causes myelin breakdown. This promotes Aβ oligomerization and deposition, potentiating Aβ toxicity (Bartzokis et al. 2007). There exists another group of glial cells termed oligodendroglial precursor cells (OPCs) in the brain which express NG2 (a chondroitin sulfate proteoglycan) and are therefore called NG2 cells (Xu et al. 2011). NG2 cells are majorly responsible for Aβ uptake and its clearance by the lysosomal pathway (Li et al. 2013). In patients suffering from Alzheimer's, the number of NG2 cells is reduced which diminishes Aβ clearance and thus increases its deposition contributing to AD progression. Astrocytes are widely distributed throughout the CNS, playing roles such as elimination of neuronal debris, excitability of neurons, defense against oxidative stress through production of glutathione, prevention of neuronal toxicity by glutamate homeostasis, and synaptic development and plasticity (He and Shen 2009; Finsterwald et al. 2015; Khakh and Sofroniew 2015). In AD, there is marked oligomeric amyloid-β generation which gives rise to astrocytes with a reactive phenotype and thus there is abnormal regulation of the processes mediated by astrocytes. This results in multiple negative outcomes which include glutamate excitotoxicity, impaired synaptic plasticity, oxidative stress, etc. (Crystal et al. 2017).

13.2.5 Oxidative Stress in Alzheimer's Disease

Oxidative stress occurs because of variety of molecules and free radicals derived from molecular oxygen collectively called reactive oxygen species (ROS). Under normal conditions, there is a balance between ROS formation and antioxidant. In various pathological scenarios including the AD, antioxidant defense system of the cells is not able to cope with oxidant species which generates oxidative stress. Thus, ROS starts oxidizing many cell structures and molecules which deteriorates them and leads to aging. Other important reasons for increased ROS production are mitochondrial dysfunction and chronic inflammatory responses occurring in AD. Apart from this, oxidative stress also increases β-secretase and γ-secretase activity, thus increasing Aβ formation (Cervellati et al. 2016).

13.2.6 Apolipoprotein E and Alzheimer's Disease

Apolipoprotein E (ApoE) produced by astrocytes in CNS is majorly involved in lipid transport and injury repair in the brain. The ε4 allele of the APOE is the strongest risk factor for late-onset AD and ε2 form may decrease one's risk (Corder et al. 1993). All ApoE isoforms have different ability to bind lipids and Aβ. The ε3 form is the most common. The ε4 form is the next most common, and the ε2 form is the least common (Mahley and Rall 2000). It has also been shown in some studies that APOE genotypes vigorously show deposition of Aβ to form senile plaques and cause cerebral amyloid angiopathy (CAA) (Ellis et al. 1996). The Aβ deposition in the form of senile plaques is more abundant in APOE ε4 carriers compared with noncarriers (Kok et al. 2009).

13.2.7 NMDA (Glutamate) Receptor

The N-methyl-D-aspartate receptors (NMDARs) are cationic channels gated by the neurotransmitter glutamate which play an essential role in excitatory transmission, learning, and memory in the central nervous system (CNS) (Kamat et al. 2013). Glutamate levels are maintained in the CNS by astrocytes which uptakes and metabolizes excessive glutamate from synaptic cleft. In AD patients, the ability of astrocytes to uptake and metabolize glutamate is decreased, causing chronic excess of glutamate levels and thus overactivation of NMDA receptors. This causes excessive calcium (Ca2+) influx in response which causes mitochondrial functional impairments and ROS formation (Koleske 2013). ROS oxidizes many cell structures and molecules leading to aging while sudden and excessive Ca2+ influx causes series of events leading to cell death including neurotoxicity. Thus, improper NMDA receptor may participate in the pathogenesis of AD (Kamat et al. 2013).

13.3 Treatment for Alzheimer's Disease

The pharmacotherapy of AD utilizes cholinesterase inhibitors and NMDA receptor antagonists which provide only symptomatic relief. Permanent cure of AD still remains elusive. It is imperative that drugs used for treatment of Alzheimer's disease should be able to cross the blood-brain barrier (BBB) and reach the central nervous system before the therapeutic effect can be exerted. The first choice for the treatment is choline esterase inhibitors (ChEIs) which are meant to prevent degradation of acetylcholine in the synaptic cleft, important for learning and memory. Widely used ChEIs include oral tacrine, donepezil, rivastigmine, galantamine, as well as rivastigmine patches. It has also been hypothesized that in AD, glutamate causes excessive and nonphysiological activation of NMDA receptors, thus causing excitotoxic neuronal damage. In 2003, the USFDA approved memantine, a moderate and noncompetitive NMDA receptor antagonist for the treatment of moderate to severe stages of AD. A combination of one of the cholinesterase inhibitors, e.g., donepezil with memantine, is also being prescribed.

13.3.1 Disease-Modifying Agents

Sixty-three percent of drugs which are under testing or trials are called disease-modifying therapies (DMTs). This means that they not only work to reduce current symptoms, but rather to improve outcome over a longer period of time. Most of the DMTs which are under trials work either to reduce amyloid levels in the brain or to decrease its production or they work on tau proteins (Cummings 2017). The major categories of disease-modifying agents are described in the following section.

13.3.1.1 Amyloid Treatment

Various approaches have developed to slow or prevent amyloid aggregation and improve clearance from the brain. These include immunotherapy and enzyme inhibitors. Some of the anti-amyloid approaches are described below.

Active and Passive Immunotherapy
In transgenic AD mouse models, anti-Aβ antibodies were generated by active immunization. It was seen that at the preclinical AD stage or at the onset of AD-like pathogenesis, brain Aβ levels were lowered significantly but with well-established AD-like pathology, effects were variable. A second-generation safer vaccine, ACC-001, is currently in phase II clinical trials in patients with mild to moderate AD and it has no adverse effects such as aseptic meningoencephalitis which were observed in 6% of patients after the administration of first-generation amyloid vaccine AN-1792 (Lemere and Masliah 2010).

Monoclonal Antibodies (mAbs)
mAb*s* are antibody solutions which are injected intravenously. These are highly specific to the Aβ deposits in the brain and therefore initiate an immune response against them by increasing their uptake by the microglial cells (Robert and Wark 2012). For this to happen, anti-Aβ antibodies should cross the BBB and bind Aβ within the CNS or by "sink effect," it could bind with Aβ peptide in the blood that would "draw" the peptide from the brain to the periphery through the BBB (DeMattos et al. 2001). Bapineuzumab, crenezumab, gantenerumab, solanezumab, and others are the drugs belonging to this class (Robinson 2015). A phase II clinical trial of bapineuzumab showed that it decreased both total and phosphorylated tau levels in CSF but did not affect Aβ level with adverse effects being transient cerebral vasogenic edema in some patients. Most of immunotherapy decreased cognitive decline and reduced beta-amyloid load, but the adverse events still need to be solved.

BACE Inhibitors
Drugs have been developed to reduce beta-amyloid production that inhibit the activity of an enzyme called β-site APP-cleaving enzyme (BACE) which generates beta-amyloid protein from APP. Among the BACE inhibitors in testing are verubecestat, LY3314814, CNP520, and others. Small molecule inhibitors of secretases are nonspecific, while larger molecules which are more specific have very less BBB permeation (Cummings 2017). These agents are only useful if started early in the disease process, which is well before most AD patients are diagnosed.

γ-Secretase Inhibitors/Modulators
γ-Secretase inhibitors like DAPT decreased Aβ levels in plasma and cerebrospinal fluid (CSF) of AD mice/rats. Another γ-secretase inhibitor semagacestat (LY450139) dihydrate reduced Aβ levels in serum but not in the CSF. Notch, which is necessary for growth and development, is also a substrate of γ-secretase. Notch-related side effects of γ-secretase inhibition (e.g., severe gastrointestinal and hemopoietic side effects, neurodegeneration) are the biggest problems in developing useful γ-secretase inhibitors. Thus, there is a shift of drug development toward γ-secretase modulators (Karran et al. 2011).

α-Secretase Activators/Modulators
Since α-secretase and β-secretase work on the same substrate APP, Aβ secretion can be decreased by upregulating the activity of α-secretase which will decrease the amount of APP available for β-secretase and thus have therapeutic potential. Members of the adamalysin family of proteins, mainly ADAM 10, ADAM 17, and ADAM 9, fulfill some of the criteria required of α-secretase. ADAM10 was overexpressed in transgenic mice which showed less amyloid deposition as well as improved neurological function (Postina et al. 2004). Deprenyl and PKC activator TPPB can also increase α-secretase activity and decrease Aβ secretion (Yang et al. 2009). This implies that stimulating α-secretase may have benefit but no clinical data is available at present.

Peptide Inhibitors of Amyloid Aggregation
Tjernberg et al. (1996) used amyloid peptide fragment KLVFF as an aggregation inhibitor. Although aggregation was still seen, a significant decrease in fibrillization led to designing of another peptide inhibitor, called OR2, which was designed from the KLVFF sequence and could modify early aggregation of Aβ as well as protect SHSY-5Y cells from Aβ cytotoxicity (Pallitto et al. 1999).

M1 Muscarinic Agonists
Activation of M1 mAChRs with agonists leads to either enhanced secretion of sAPPα (via α-secretase activation) or decreased Aβ (via γ-secretase inhibition). Talsaclidine is M1 agonist that stimulates α-secretase activity in vitro so when given to AD patients in a clinical study, it decreased CSF Aβ about 20% compared with the baseline (Hong 2012).

Aβ Aggregation Inhibitors
Intra-hippocampal injection of β-sheet breaker iAβ5p not only improved memory but also decreased amyloid plaques (Hong 2012). Tramiprosate also inhibited the formation of neurotoxic aggregates in the brain but it failed in US phase III trial in 2007. Resveratrol, myricetin, morin, tannic acid, curcumin, ferulic acid, nordihydroguaiaretic acid (NDGA), and (−)-epigallocatechin gallate (EGCG) had strong anti-Aβ aggregation effects in vitro. Colostrinin (CLN) isolated first from ovine colostrums improved learning, memory, and cognitive functioning as it inhibited the aggregation of Ab peptides and dissolved pre-formed fibrils.

Aβ-Degrading Enzymes
Studies show that Aβ peptide can be degraded by proteases called Aβ-degrading enzymes like neprilysin (NEP), insulin-degrading enzyme (IDE), plasmin, endothelin-converting enzyme (ECE) 1 and 2, and angiotensin-converting enzyme (ACE). Less Aβ degradation and declining cognition was seen in NEP inhibitor injected and/or NEP knockout mice, while overexpression improved spatial memory and decreased Aβ levels. Studies have shown that APP intracellular domain (AICD) could upregulate NEP transcription and thus increase Aβ degradation (Belyaev et al. 2009). Imatinib was shown to elevate AICD in H4 human neuroglioma cells and thus increase of NEP activity as well (Bauer et al. 2011).

13.3.1.2 Treatments Based on Tau Pathology

Tau phosphorylation increases drastically in AD, indicating tau kinase inhibitors could be used as an anti-AD treatment. Tau aggregation inhibitors and immunotherapy also could be viable approaches for AD therapy.

Glycogen Synthase Kinase (GSK)-3β
It is well established that this kinase can phosphorylate tau in cells in culture and in the brains of transgenic mice. In animal models kinase is blocked by lithium, preventing tau phosphorylation (Roberson and Mucke 2006). The M1 muscarinic agonist AF267B also inhibits GSK-3β activity and thus reduces tau phosphorylation in

transgenic mice. Two additional inhibitors are propentofylline (PPF) and SRN-003-556. Finally, activated MAPK has been reported to be associated with neurofibrillary tangles (NFTs) in human AD (Husain et al. 2008). Its inhibitors could have a role in AD treatment.

Preventing Tau Aggregation
Studies show that some inhibitors not only prevent tau protein aggregation but can also dissolve the already formed aggregates, which include phenothiazines, anthraquinones, polyphenols, thiacarbocyanine dyes, thiazolyl-hydrazides, rhodanines, aminothienopyridazines, and so on (Ballatorea et al. 2011). Studies in vivo are still needed to find the efficacy and safety of tau aggregate inhibitors.

Prevention of the Misfolding of Tau
Misfolding of hyperphosphorylated tau proteins also contributes to AD. It is well known that heat shock protein 90 (Hsp 90), a chaperone, folds the denatured proteins and it has a role in preventing tau degradation under normal conditions. Curcumin is also reported to inhibit Hsp 90 which under pathological conditions degrades tau in spite of preventing it (Giommarelli et al. 2010).

Tau Immunotherapy
Asuni et al. (2007) demonstrated that immunization of mice expressing P301L-tau (JNPL3 mice) with a small phospho-tau peptide resulted in the production of antibodies that entered the brain and slowed the progression of the behavioral phenotype. Thus a passive immunization may be a better therapeutic approach.

13.3.2 Oxidative Stress and Antioxidants

Acrolein, the by-product of lipid peroxidation, as well as markers of oxidative stress such as heme oxygenase-1 was found to be elevated in brains from patients with AD, which indicates that oxidative damage has an early role in the pathogenesis of AD (Schipper et al. 2006; Nam et al. 2010). Interestingly, in vitro and in vivo studies reported that oxidative markers are decreased by the administration of different polyphenolic compounds such as catechins, curcumin, or resveratrol (Singh et al. 2008).

Catechins
Green tea which belongs to a class of polyphenol has epigallocatechin gallate (EGCG) as the main active component besides (−)-epigallocatechin (EGC), (−)-epicatechin (EC), and (−)-epicatechin-3-gallate (ECG) (Moyers and Kumar 2004). Green tea extract protects neurons from the Aβ-induced damages because ECGC modulates various pathways such as MAPK, PKC, and phosphatidylinositol-3-kinase (PI-3 kinase)-Akt (Chen et al. 2001; Levites et al. 2003; Koh et al. 2003). Though its instability in solution and degradation through oxidative processes needs to be resolved.

Curcumin

It is used as spice in India and it is extremely safe even at very high doses. Curcumin blocked Aβ aggregation in vitro (IC50 = 0.8 μM). In vivo, in Tg2576 mice, reduction of amyloid plaque burden was observed after curcumin treatment (Yang et al. 2005). Moreover, curcumin could chelate the redox active metal iron and copper which have a role in AD pathogenesis. However, its extremely low aqueous solubility, rapid systemic elimination, and inadequate tissue absorption, which severely retards its bioavailability need to be addressed (Anand et al. 2007).

Resveratrol

Resveratrol (trans-3,4,5-trihydroxystilbene) is the main biologically active non-flavonoid found in grapes and red wine (Baum and Ng 2004). Some studies show less incidence of AD with increasing wine consumption. Not only resveratrol protected PC12 cells against Aβ-induced toxicity but the secretion of Aβ was also reduced in two cell lines, HEK 293 and N2a (Jang and Surh 2003; Marambaud et al. 2005). Its protective effect may be due to specific activation of Sirt1 (Kaeberlein et al. 2005). However, it is rapidly metabolized in liver and intestinal epithelial cells so its bioavailability needs to be addressed.

In summary, polyphenolic compounds such as catechins, curcumin, or resveratrol are safe and have protective properties but their efficacy in humans is not yet definitively proved as no clinical trials have been completed yet.

13.3.3 Chelating Agents

Concentration of metal ions such as copper (390 μM), zinc (1055 μM), and iron (940 μM) are elevated by several-folds in AD brain as compared to normal samples [copper (70 μM), zinc (350 μM), and iron (340 μM)] (Adlard and Bush 2006). Zinc and the iron regulatory protein-2 have been found to co-localize with NFT-containing neurons. Ferric ions and cupric ions bind to various "repeat" motifs on tau increasing its phosphorylation and aggregation. Therefore, metallo-complexes are emerging as a new target for AD. It has been observed in phase 2 clinical trial that clioquinol reduces the rate of cognitive loss due to its ability to chelate zinc and copper associated with amyloid plaques (Hong 2012).

13.3.4 Nicotine

Nicotine is a cholinergic agonist to release acetylcholine, which is an alkaloid derived from the leaves of tobacco plants (Graham et al. 2002). Nicotinic receptor densities are decreased in neurodegenerative disorders such as AD. Nicotine showed significant improvements in several cognitive tasks and in mood although not on memory when injected on people with AD (Court et al. 2005). It is also believed that

nicotine has a preventive action on AD. Adverse effects of cardiovascular risks in elderly people, sleep, and behavior need to be worked to further study the use of nicotine in patients with AD.

13.3.5 Melatonin (N-Acetyl-5-methoxytryptamine)

It is a neuroprotective tryptophan metabolite, synthesized by the pineal gland. It regulates circadian rhythms, removes free radicals, etc. (Wu and Swaab 2005). In AD patients, there are decreased levels of melatonin in serum and in CSF (Rosales et al. 2012). It inhibits the amyloid beta aggregation as well as prevent the hyperphosphorylation of the tau protein in rats indicating that melatonin may be used in AD (Wang et al. 2005).

13.3.6 Cell Transplantation and Gene Therapy

As cholinergic hypothesis is associated with the pathology of AD, transplantation of cholinergic-rich tissue or peripheral cholinergic neurons was done in AD rat model which improved behavior and cognitive function (Chen et al. 1997). Lack of endogenous nerve growth factor (NGF) can lead to memory deficits so fibroblasts genetically modified to express human NGF were transplanted into the forebrain of eight patients with mild AD and it was seen that cognitive decline was improved as evidenced by the MMSE and AD Assessment Scale. Cerebrolysin 1 (Ever Neuro Pharma) which possesses neurotropic properties has been combined with AChEI and it was shown to have synergistic effects in AD (Allegri and Guekht 2012).

13.3.7 Cholinergic Precursors

Cytidine 5′-diphosphocholine (CDP-choline) and choline alphoscerate are precursors of choline and increase acetylcholine content and release. CDP-choline 9 (citicoline) is a prescribed drug in several European countries and in Japan. Further studies are required on CDP-choline efficacy on memory. Choline alphoscerate can probably cross the BBB and enter nerve cell membranes within 24 h of absorption. A review of 13 clinical trials concluded that it should be confirmed in future investigations for dementia (Sahni 2011).

13.3.8 Monoamine Oxidase (MAO) Inhibitors

MAO inhibitor deprenyl besides being an anti-Parkinson drug has also been used in AD for many years. It is known through in vitro experiments that deprenyl has a role in APP processing through PKC and mitogen-activated protein kinase (MAPK) signaling pathways. Another MAO-B inhibitor rasagiline also inhibits acetylcholinesterase besides APP processing, through PKC and MAPK pathways. Ladostigil is a dual acetylcholine butyrylcholinesterase. It increases cholinergic neurotransmission and is also a brain selective MAO-A and MAO-B inhibitor. It thus shows neuroprotective effects in vivo in scopolamine-induced impairment in spatial memory (Weinreb et al. 2012).

13.3.9 Miscellaneous Agents

Medications for noncognitive behavioral symptoms such as apathy, agitation, and sleep disturbances include the antidepressants escitalopram and mirtazapine, the cannabinoids nabilone and dronabinol, the anticonvulsants carbamazepine and levetiracetam, the novel antipsychotic pimavanserin, the combination of dextromethorphan and quinidine, the mood regulator lithium, and the stimulant methylphenidate. The use of other agents like nonsteroidal anti-inflammatory drugs (NSAIDs) such as celecoxib or indomethacin, phenserine, statins, tarenflurbil, tramiprosate, *Ginkgo biloba*, vitamin E, selegiline, estrogens, and pentoxifylline for the treatment of AD is not recommended yet because of inconsistent results. However, there have been several trials but more studies are still needed to establish whether or not they have any role in treatment of AD (Grossberg 2019). For instance, estrogen when given during hormone replacement therapy (HRT) has also worked as a neuroprotective agent for AD. However, Shumaker and colleagues reported in a study that postmenopausal women treated with estrogen plus progestin were at increased risk for dementia. Thus, for further investigations, studies in AD with estrogen analogues (e.g., premarin, raloxifene) are now mostly in phase II (Shumaker et al. 2003).

The dye methylene blue prevents tau interactions as well as inhibits Aβ aggregation, decreases oxidative stress, prevents mitochondrial damage, and inhibits AChEs. As Aβ oligomers activate various intracellular pathways, drugs that interrupt these signaling pathways could be useful in AD. Recently, it has been reported that rolipram which is a PDE-4 selective inhibitor effectively reversed memory defects in Ab-treated mice. Some studies have reported that if chronic growth factor is deprived for a longer duration, the GABA transmission changes from inhibitory to excitatory stimulus. SGS742 is a GABAB antagonist which is in phase II trial stage and showed good results in phase I trials. Areas of the brain involved in learning and memory have high levels of 5-HT1A, 5-HT4, 5-HT6, and 5-HT7 receptors.

Many 5-HT4 agonistic compounds like PRX-03140, velusetrag, and others have positively affected cognition in animal models as well as affected amyloid processing. Neural stem cell (NSC) engraftment is believed to have a role in AD since NSCsβ are responsible for producing various factors such as neurotrophic factors that promote the regeneration of the CNS (Blurton-Jones et al. 2009; Kumar 2015). Administration of DHA in mild to moderate AD showed no delay in the rate of cognitive decline according to the MMSE.

Despite existence of knowledge regarding this complex disease, very few options are available for its management. BACE inhibitors offer a promising approach, but only few drugs have undergone clinical trials as of now. γ-Secretase, another enzyme involved in Aβ production, can also be targeted but side effects associated with notch inhibition are posing problems. So far, the vaccination approach remains promising because of behavioral improvements in mice. Some novel approaches such as DNA vaccination, NOS modulation, or caspase inhibition are also available but they still are needed to be studied. Peptide-based inhibitors present an alternative and appealing preventative strategy to MAb therapies, as they are not as costly to produce, versatile, and intrinsically safer and can be easily modified for superior BBB permeation.

13.4 Drug Delivery Approaches for Targeted Delivery of Anti-Alzheimer Drugs

Although a variety of therapeutic approaches have been tried in treatment of AD, very few have been successful in the clinical trials. The main reasons attributable to the therapeutic failure of many such drug candidates are poor or low oral bioavailability and inability to cross the blood-brain barrier (BBB). Conventional delivery of acetylcholinesterase inhibitors (AChEIs) like tacrine, donepezil, and rivastigmine is associated with side effects attributable to peripheral cholinergic effects. Most frequently reported side effects include nausea, vomiting, and diarrhea which many a time lead to discontinuation of therapy (McGleenon et al. 1999). Tacrine has been discontinued in the US market since 2013 owing to safety concerns. Brain-targeted delivery can be a viable option for delivery of the therapeutic moiety directly to its target site without any peripheral side effects. In the recent times nanotechnology has emerged as a potential tool for targeted delivery of drug molecules to its site of action including the central nervous system. The potential advantages that nanoparticulate carriers can offer include long circulation half-life, controlled release of the encapsulated drug, ability to cross biological membranes intact, and amenability to surface modification and ligand attachment for targeting. Emergence of nanotherapeutics has contributed a lot in development of various nanosystems like liposomes, polymeric and solid lipid NPs (SLNs), solid lipid carriers, liquid crystals (LCs), microemulsions (MEs), and hydrogels. Different types of nanoparticles have been utilized for targeted delivery to the brain including polymeric nanoparticles, lipid-based nanoparticles, inorganic nanoparticles, and dendrimers (Fig. 13.3). Different

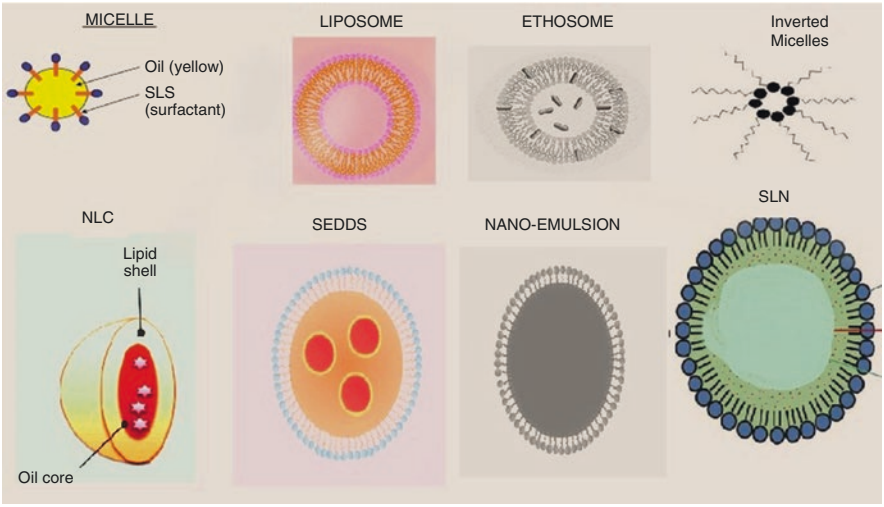

Fig. 13.3 Types of nanolipidic carriers

routes of delivery can be utilized for administering the drug-loaded nanoparticles to the body including parenteral, intranasal, pulmonary, and oral (Saraiva et al. 2016).

Polymeric Nanoparticles

Polymeric nanoparticles constitute the particulate dispersions or are solid particles having a size in range of 1 nm –1000 nm. These particulates may be either in capsular or matrix form depending upon organization of oily or aqueous composition and polymers. Several methods of formulation and development of such NPs have been established like polymerization, ionic gelation and coacervation, emulsification and solvent evaporation, solvent diffusion, nanoprecipitation, spray drying, etc. It has been observed that NPs cross the BBB easily and exhibit increased retention in blood capillaries of the brain which leads to a higher concentration gradient across the endothelial cell layer and thus enhanced delivery of drug to the brain. Further it has been investigated in several experiments that usage of surfactant may solubilize the lipids of the endothelial cell membrane and enhance drug permeability across the BBB. Other fabrication methods including coating NPs with polyethylene glycol (PEG) polymers, or antibodies or mucoadhesive polymers, can increase the retention time of NPs when administered via nasal route (Masserini 2013).

Solid Lipid Nanoparticles (SLN)

SLNs are specifically solid carriers comprising solid lipid core matrix of triglycerides (e.g., tristearin), diglycerides (e.g., glyceryl behenate), monoglycerides (e.g., glycerol monostearate), fatty acids (e.g., stearic acid), steroids (e.g., cholesterol), or waxes (e.g., cetyl palmitate). Generally production of these particles requires stabilization by surfactants to prevent particle agglomeration. Recently a new category of NPs has been developed utilizing a blend of solid lipids in combination with

liquid lipids, namely, nanostructured lipid carriers (NLCs). The primary composition of SLNs or NLCs comprises lipids, emulsifier, and water or solvent and different methods of their preparation are high-pressure homogenization, ultrasonication, high-shear techniques, solvent evaporation, solvent emulsification-diffusion, supercritical fluid method, spray drying, double emulsion and precipitation technique, etc. It has been investigated that these carriers are efficient enough to penetrate and cross BBB easily upon administering through nasal route. Further modifications like use of cationic lipids or coating with surfactants can improve mucoadhesion and thus efficient drug delivery. The advantages that SLN/NLCs offer over polymeric nanoparticles include low cost, easy fabrication, biocompatibility, and high encapsulation efficiency for both lipophilic and hydrophilic drugs (Sonvico et al. 2018).

Recently, Jojo et al. (2019) have evaluated pioglitazone, an antidiabetic drug, for its potential activity in treatment of AD. They optimized the formulation of pioglitazone in the form of nanolipid carriers (NLCs) to target the brain via intranasal route. The in vitro drug release of NLCs was reported to show a sustained release pattern and it was also claimed for improved nasal permeability ex vivo. The toxicity studies conducted confirmed the safety of formulation for the in vivo administration.

In a recent research by Soroor et al. (2019), SLNs and NLCs of curcumin were formulated and targeted to the brain for free radical scavenging in AD. They reported that antioxidant property of curcumin can significantly alter the oxidative stress in AD; however, its targeting to the brain and bioavailability is a big challenge. It was concluded that NLCs and SLNs prepared were capable of crossing BBB. Further, they claimed that upon i.v. administration of free curcumin, SLNs and NLCs, the NLCs were found to be the most bioavailable. The DPPH (2,2-diphenyl-1-picrylhydrazyl) free radical scavenging study indicated that preparation processes do not have any significant effect on the antioxidant activity of curcumin.

In 2018, Vakilinezhad and coworkers studied the role of nicotinamide in halting AD progression. They prepared nicotinamide-loaded solid lipid nanoparticles (SLNs) functionalized with polysorbate 80 (S80) or phosphatidylserine (PS) or phosphatidic acid (PA). Further the SLNs were evaluated for cytotoxicity, biodistribution, and in vivo effectiveness through the different routes of administration. Also the spatial memory test, histopathology, and biochemical tests were conducted which confirmed effectiveness of PS-functionalized SLNs in improving the cognition, preserving the neuronal cells, and reducing tau hyperphosphorylation in a rat model of Alzheimer's disease.

Liposome

Liposomes are vesicular DDS comprising of one or more phospholipid bilayers over aqueous core and are capable of carrying both lipophilic and hydrophilic drugs. Different methods utilized in preparation of liposomes are sonication, extrusion, high-pressure homogenization and reverse-phase evaporation, etc. Depending upon the number of lipid layers over aqueous core, liposomes may be unilamellar or multilamellar. Further, liposomes can also be of different types according to their fabrication methods and materials used in fabrication, e.g., niosomes, transfersomes,

ethosomes, and phytosomes. Several strategies have been utilized for efficient targeting of liposomes across the BBB including coating and conjugation with certain chemicals or biomolecules. This is also termed as functionalization of liposomes that leads to enhanced uptake and permeability of these carriers across various barrier models. In vivo uptake studies have also been performed in animal models of AD to demonstrate the effectiveness of these nanosystems.

Nowadays health supplements and natural products are emerging as one of the efficient strategies in modulation of therapy of AD. Recently, Yaseen et al. (2018) evaluated the protective effect of nano-wheat germ (NWG) and nano-rice bran (NRB) in AD. The study was conducted in rats having dyslipidemia. Various parameters like lipid profile, level of butyrylcholinesterase (BChE), brain oxidative stress, and inflammatory biomarkers were assessed. The results of biochemical and nutritional parameters reported significant improvement in oxidative stress management in AD.

According to another study, Loureiro et al. (2017) reported that various natural compounds like resveratrol possess potential neuroprotective characteristics that can be utilized in treatment of AD. Evaluation of grape skin seed extracts was done for resveratrol content and tested for its activity for inhibition of Aβ aggregation in the brain. To avoid metabolism and increase bioavailability of resveratrol in the brain, solid lipid nanoparticles (SLNs) functionalized with an anti-transferrin receptor monoclonal antibody (OX26 mAb) were prepared. The results demonstrated active targeting of brain by the fabricated SLNs with massive improvement in AD progression. Some of the recent research works utilizing lipid-based nano-carriers for brain-targeted delivery of anti-Alzheimer drugs are summarized in Table 13.1.

13.5 Role of BBB in CNS Targeting

The hindrance in effective treatment of AD is not just because of the lack of efficacy of drugs but also due to their inability to cross the BBB. Therefore, in order to target delivery of drugs to the brain, it is very important to learn about BBB.

The BBB acts as a mediator between the CNS and the peripheral blood circulation. It is a highly selective physical as well as chemical barrier whose function is to prevent the entry of unwanted foreign molecules and pathogens into the brain while allowing the influx of necessary nutrients, signaling molecules, and immune cells into the brain. BBB is formed by endothelial cells on the blood side and astrocytes and pericytes on the brain side (Chen and Liu 2012). The endothelial cells of the BBB possess an increased number of mitochondria and they form tight junctions (TJs) in association with tight junction proteins such as occludins, claudins, and junctional adhesion proteins which itself are induced by zonula occludens proteins (ZO-1/2/3) and cingulin (Pardridge 2003). The high number of mitochondria in endothelial cells provides high resistance of 1000 Ω/cm^2 which helps in transcytosis (Abbott et al. 2006; Jain 2012) where highly lipo-

Table 13.1 Recent developments in nanotherapeutics in treatment of Alzheimer's disease

S. No	Year	Technology (nanosystem)	Drug/active ingredient	Animal model/cell line	Application/advancement/findings	Reference
1.	2016	Solid lipid nanoparticles (SLNs)	Resveratrol-loaded SLNs, functionalized with apolipoprotein E	Immortalized human cerebral microvascular endothelial cells (hCMEC/D3)	Promising brain targeting of resveratrol-loaded SLNs functionalized with apolipoprotein E Least degradation in the bloodstream No toxicity up to 50 Mm size and high permeability (1.8-fold)	Neves et al. (2016)
2.	2016	Solid lipid nanoparticles (SLNs)	Astaxanthin-1	Pheochromocytoma-12 cell line	Radiolabeled nanoparticles were found to be 96–98% stable even after 48 h of labeling in phosphate-buffered saline (pH 7.4) Comparative biodistribution data indicated higher drug concentration in the brain upon intranasal administration of 99 mtc labeled astaxanthin solid lipid nanoparticles as compared to their delivery via intravenous route Studies on the pheochromocytoma-12 cell line demonstrated the antioxidant potential of astaxanthin solid lipid nanoparticles against H2O2-induced toxicity (oxidative stress)	Chandra Bhatt et al. (2016)
4.	2016	Nanoparticles and solid lipid nanoparticles (SLNs)	Tarenflurbil	Male Sprague Dawley (SD) rats	Comparative study of tarenflurbil (TFB)-loaded poly(lactide-co-glycolide) nanoparticles (TFB-NPs) and solid lipid nanoparticles (TFB-SLNs) were done to evaluate their brain targeting efficiency through intranasal route Brain targeting efficiency was determined in terms of %drug targeting efficiency (%DTE) and drug transport percentage (DTP). The higher %DTE (287.24) and DTP (65.18) were observed for TFB-NPs followed by tfbSLNs (%DTE, 183.15, and DTP, 45.41)	Muntimadugu et al. (2016)

5.	2016	Solid lipid nanoparticles (SLNs)	Chrysin (CN)	Rats with amyloid-β_{25-35}-induced oxidative stress in their hippocampal region	Chrysin SLNs (CN-SLNs) were prepared and investigated for their therapeutic role in neuronal damage upon administration of Aβ25–35 All the antioxidant enzymes and nonantioxidant enzyme in hippocampus were reduced significantly ($P < 0.01$) in the Aβ25–35-injected group, whereas lipid peroxidation and acetylcholine esterase were increased significantly ($P < 0.01$) Claimed for better therapeutic efficacy of CN-SLNs at lower dose as well as high bioavailability	Vedagiri and Thangarajan (2016)
6.	2016	Nanostructured lipid carriers (NLC)	Temozolomide	Mouse/mice injected with TMZ-dispersion (i.v.) and treated with TMZ-NLCs (intranasal)	Prepared a range of TMZ-NLC formulations having sizes in the nanometer range, with high drug loading and prolonged drug release In vivo studies in mice showed that the brain/blood ratio of TMZ-NLC was significantly high, also confirmed by scintigraphy images of mouse brain The AUC ratio of TMZ-nlct to TMZ-disp in the brain was the highest among the organs	Khan et al. (2016)
3.	2015	Solid lipid nanoparticles (SLNs)	Galantamine hydrobromide	Cognitive deficit rats	The SLNs formed were of nanocolloidal range (lower than 100 nm) having drug entrapment up to 83.42 ± 0.63%. And more than 90% drug release in vitro within 24 h In vivo evaluations demonstrated significant memory restoration capability in cognitive deficit rats in comparison with naive drug The developed carriers offered approximately twice bioavailability to that of plain drug	Misra et al. (2015)

(continued)

Table 13.1 (continued)

S. No	Year	Technology (nanosystem)	Drug/active ingredient	Animal model/cell line	Application/advancement/findings	Reference
8.	2013	Nanocapsules	Resveratrol	Male adult Wistar rats (300–350 g) with impaired cognitive functions induced by i.c.v. injection of Aβ1–42	Comparative analysis of neuroprotection provided by free resveratrol versus resveratrol-loaded lipid-core nanocapsule treatment against intracerebroventricular injection of Aβ1–42 in rats Claimed for robust increase of resveratrol concentration in the brain tissue by lipid-core nanocapsules	Frozza et al. (2013)
9.	2013	Liposomes	Rivastigmine	Male albino rats of Wistar strain weighing 260 ± 20 g having deterioration of spatial memory induced by AlCl3	Comparative analysis of rivastigmine liposomes (RLs) w.r.t rivastigmine solution (RS) against aluminum chloride (AlCl3)-induced Alzheimer's model Both RLs and RS improved the deterioration of spatial memory induced by AlCl3, with RLs having a superior effect The profound therapeutic effect of RLs over RS was evidenced by nearly preventing amyloid plaque formation	Ismail et al. (2013)

7.	2012	Nanocapsules	Indomethacin	Male adult Wistar rats (280–330 g) with impaired cognitive functions induced by i.c.v. injection of Aβ1–42	Investigated the potential protective effect of indomethacin-loaded lipid-core nanocapsules (indoh-lncs) against cell damage and neuroinflammation induced by amyloid beta (Aβ)1–42 in AD models Results showed that indoh-lncs attenuated Aβ-induced cell death and blocked the neuroinflammation triggered by Aβ1–42 in organotypic hippocampal cultures Also indoh-LNC treatment led to the increase in interleukin-10 release and decrease glial activation and c-jun N-terminal kinase phosphorylation	Bernardi et al. (2012)
10.	2009	Solid lipid nanoparticles (SLNS)	Ferulic acid	LAN5 cell line	Preparation of SLNS of ferulic acid (FA), a phenolic compound with a significant antioxidant activity in Alzheimer's disease Cells treated with FA-loaded SLN showed a higher reduced reactive oxygen species production than cells treated with free FA	Bondì et al. (2009)

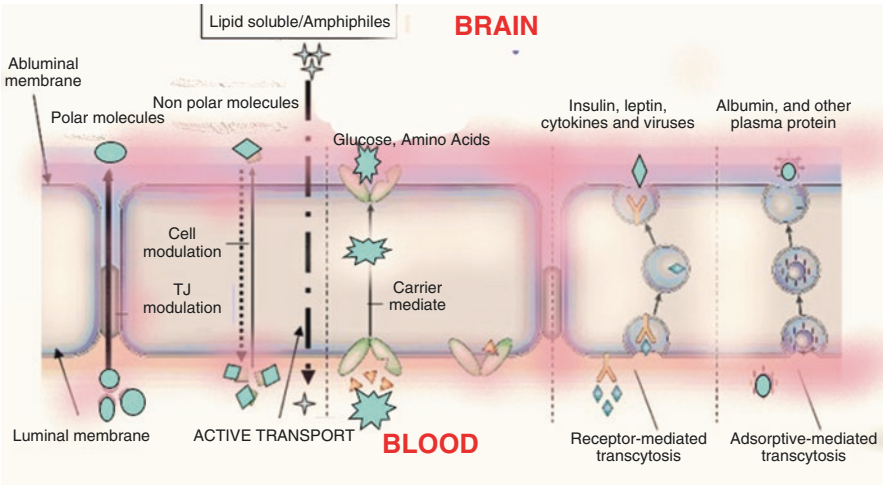

Fig. 13.4 Transport mechanism across blood-brain barrier

philic molecules with a molecular weight <600 g/mol and oxygen and carbon dioxide can easily pass through by passive diffusion, and brain nutrients (i.e., glucose, amino acids) that are highly hydrophobic pass through special transporter proteins actively, while certain larger molecules (i.e., insulin, iron transferrin) tend to pass through receptor-mediated transportation. The different mechanisms of transport by which endogenous and exogenous molecules can travel across BBB are illustrated in Fig. 13.4.

Endothelial cells, astrocytes, and pericytes work together to maintain the integrity of BBB. Astrocytes release some factors, such as transforming growth factor-β (TGF-β) and interleukin-6 (IL-6), which enhance expression of cell signaling proteins such as P-glycoprotein and many others on endothelium (Abbott et al. 2006). Pericytes are involved in endothelial cell growth regulation. Pericytes and endothelial cells are covered by the basement membrane which not only provides mechanical support but also helps in communication of endothelial cells with parenchyma (Dohgu et al. 2005). Endothelial cells also contain cytochrome P-450 system, monoamine oxidase, and other enzymes which prevent the entry of drugs and toxins due to their metabolization (Rubin and Staddon 1999). Besides this, some efflux transporters like P-glycoprotein (P-gp), multidrug resistance protein (MRP), and receptor for advanced glycation end products (RAGE) are also expressed at endothelium surface which actively transports unwanted materials out (Cirrito et al. 2005), while transporter proteins like glucose carrier (GLUT1) and amino acid carrier (LAT1) transport nutrients to the brain. Receptor proteins like insulin receptors, transferrin receptors (TfR), and others present on the blood side of the brain influx larger molecules (mostly peptides, proteins, and lipids) into the brain (Mehta et al. 2013).

13.5.1 How BBB Breakdown Affects Drug Delivery

In AD animal models, BBB dysfunction has been associated with decreased activity of P-gp transporter. As a result, P-gp, which is involved in Aβ efflux under healthy conditions, starts accumulating Aβ in the brain (Chiu et al. 2015). BBB disruption does not increase permeability of drugs across BBB, as drugs can only cross the BBB if the blood vessels are healthy and there is adequate blood flow with recruitment of solute carrier-mediated transport (CMT) and receptor-mediated transcytosis (RMT) systems to facilitate drug delivery. It has been observed that, in the regions of pathological BBB disruption, functional and structural changes in the blood vessels such as perivascular accumulation of blood-derived fibrinogen, thrombin, albumin, immunoglobulin G (IgG), pericyte and endothelial degeneration, RBC extravasations, reduced expression of tight junctions at the BBB, increased endothelial bulk flow transcytosis, disrupted BBB transporter expression, inflammation and immune responses, occur. All of these changes prevent the entry of therapeutic agents to the brain (Chiu et al. 2015; Sweeney 2018). The disrupted BBB enables blood-derived debris and cells to accumulate in enlarged perivascular spaces. These accumulations prevent the normal distribution of molecules throughout the CNS and interrupt the regional formation of interstitial fluid (ISF) and ISF flow, which prevent therapeutic antibodies, proteins, peptides, gene medicine, and other drugs from effectively reaching their neuronal targets. Besides this function of CMT and RMT systems is also decreased which further complicates the therapeutic drug delivery process (Nelson et al. 2016). Therefore, for the successful delivery of therapeutic agents into the brain of AD patients, healthy blood vessels are needed.

13.5.2 Transport Mechanism of Nanolipidic Carriers Across BBB

Generally, most of the lipid-based nanocarriers are grouped into two major classes: nanoparticles (NPs) and liposomes (LPs). Though LPs are well known for their constitution and drug-loading efficiency, still they are not capable of effectively passing through a healthy BBB. However it has been observed that upon functionalization or surface modification with polymers, polysaccharides, peptides, or antibodies, brain targeting can be achieved successfully.

Torre and Ceña (2018) reported PEGylated liposomes are prevented from being eliminated by the immune system and have a controlled bio-distribution. Furthermore, they revealed that positively charged LPs exhibit improved interactions with the cell membrane and hence promote enhanced uptake and therefore are well suited for delivering ionic drugs and genetic materials.

Holtzman et al. (2012) worked upon apolipoprotein E (ApoE) receptors and designed nanocarriers with surface modified with ApoE which were reported as highly BBB permeable and efficient in the treatment of Alzheimer's disease (AD).

In case of SLNs, the lipids present in the DDS facilitate higher entrapment of lipophilic compounds as well as their passage across BBB with ease. NLCs are a subclass of SLNs characterized with comparative high drug loading and biocompatibility.

13.5.3 Implications for Drug Therapy in AD

Current drugs, AChEIs, used in AD therapy have ease of oral administration but they are less selective and therefore also have action on peripheral tissues leading to side effects. This problem can be solved by designing drug therapies which are able to cross the BBB and deliver drugs directly into the CNS. Nanoparticles (NPs) represent a very promising approach to facilitate BBB crossing and delivering therapeutic compounds into the brain by the use of the mechanisms of transcytosis or, more specifically, a receptor-mediated pathway. The addition of polyethylene glycol (PEG; PEGylation) to NPs is the FDA-approved method which is also used now. Nanoparticle preparation of existing drugs are being designed such as liposome preparation of rivastigmine and galantamine which allow their intranasal administration with diminished adverse effects. SLN preparations of donepezil and galantamine improved cognition compared to free drug. Polymeric nanoparticle preparation of rivastigmine and galantamine with chitosan resulted in improved bioavailability and improved uptake of both the drugs in the brain after intranasal administration. Besides this, nanoliposomic preparation of herbal drugs such as curcumin retarded Aβ aggregation. Solid lipid nanoparticle preparation of resveratrol prevented Aβ peptide fibrillation (Sweeney 2018).

13.6 Conclusion and Future Prospects

According to recent studies it has been estimated that more than 12 million people worldwide are AD patients which is going to increase manifolds in upcoming years. In this scenario, scientists are working progressively in field of nanotechnology for designing and development of nanolipidic carriers which are potential vehicles for targeting CNS-related diseases. Among various routes of administration, nasal route has shown promising results to target the brain, specifically in treatment of AD. Intranasal delivery has emerged as an alternative route to oral and parenteral administration as it is a noninvasive method for direct nose to brain drug delivery bypassing the BBB. Delivery to the brain via this route occurs through the olfactory region and respiratory epithelium since the olfactory nerve cells and trigeminal nerves are in direct contact with both the nasal cavity and the CNS. Though nasal route is the best approach, however, oral, dermal, and intravenous routes can also be evaluated for administration of such nanolipidic carriers to target to the brain. It has been recorded that nanotechnology-based products are increasing in market day by

day but still clinical trials are needed to evaluate their safety and efficacy in humans. Nanolipidic carriers have the potential to emerge as the most sought-after drug delivery vehicle in the near future for targeted drug delivery in AD that could lead to improved therapeutic outcomes with reduced costs.

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