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Autism Spectrum Disorder and Alzheimer's Disease

Advances in Research

Springer

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Preface

The multifactorial biological etiology of Alzheimer's disease and autism spectrum disorder leads to distinctive perception, thinking, and learning in affected individuals, providing a more profound emphasis on the need for early diagnosis, continuous assessment of patients, proper educational methods, and social environment.

This book explores alternative solutions for autism spectrum disorder based on the theory of brain plasticity, the relationship between the gut microbiota and the central nervous system, along with genetic factors and toxic metal exposures, which are responsible for the oxidative damage resulting in a decreased ability of patients to use objects or response to auditory stimuli. It also identifies and provides the latest research on memory loss, the first sign of cognitive impairment followed by behavioral disturbances.

This book also provides the latest research towards efficient Alzheimer's disease management, including targeting the disease with symptomatic treatments such as cholinesterase inhibitors, NMDA receptor antagonists, β-secretase and γ-secretase inhibitors, α-secretase stimulators, tau inhibitors, immunotherapy, nutraceuticals, and nano drugs. Alzheimer's disease symptoms are mainly associated with a rigorous neuronal decline and the appearance of two brain lesions, senile plaques, and neurofibrillary tangles, mainly composed of Aβ and hyperphosphorylated tau protein, respectively.

This book aims to serve as a reference book for those teaching in Neuroscience, Medicine, Biochemistry, Neuroinformatics, and Nanotechnology, and professionals in occupational therapy, geriatric clinics, and rehabilitation.

Chapter 1 discuss the latest updates in dementia pathophysiology, sleep pathologies in dementia, insomnia disorder, management of sleep disorders in dementia, and treating sleep with breathing in dementia.

Chapter 2 explore the latest research insights on understanding autism spectrum disorder and Alzheimer's disease pathogenesis with the perspective of mitochondrial dysregulation as the underlying phenomenon.

Chapter 3 overview the recent advances and trends regarding autism spectrum disorder and its correlation with Alzheimer's disease and the medications approved for Alzheimer's disease, which have also been observed to be effective in autism spectrum disorder.

Chapter 4 present the potential application of the most common natural products to Alzheimer's disease treatment due to minimizing side effects compared to isolated chemical compounds.

Chapter 5 investigates the role of environmental toxicants, mercury, accelerating symptoms, and natural compounds' therapeutic potential in preventing Alzheimer's disease, focusing on the environmental toxicants as a risk factor in Alzheimer's disease pathogenesis.

Chapter 6 provide a systematic review of Alzheimer's disease, viz. factors, environmental toxicity, genetic predisposition, and ongoing treatment strategies for developing novel drugs and the use of medicinal herbs for treating Alzheimer's disease.

Chapter 7 demonstrate deeper insights into the various polyphenols that play a pivotal role in the therapeutics of Alzheimer's disease due to their antioxidant properties providing neuroprotection and their properties of easily crossing the blood-brain barrier.

Chapter 8 investigate the spectrum of ChE inhibitors and NMDAR antagonists along with other treatment options used in Alzheimer's therapy.

Chapter 9 discuss the clinical features of psychotic illnesses, the relationship between these disorders with genetic insight, and the common therapeutic targets for these conditions.

Chapter 10 review the representation, visualization, and mathematical formulation mostly of RNA secondary structures, which can be viewed as steps towards the three-dimensional prediction modeling and their role in neurodegeneration.

Chapter 11 emphasize the current immune-therapeutics for treating Alzheimer's disease and autism spectrum disorder that have reached clinical trials and the connecting mechanisms involved in the aggregated/toxic proteins, such as amyloid-β peptide (Aβ), Aβ precursor protein (APP), tau, α-synuclein, and apolipoproteins.

Chapter 12 discuss the applications of nanoparticles in treating Alzheimer's disease, allowing the design of clever therapeutic carriers, which can simultaneously cross the blood-brain barrier and carry payloads to the specific objectives targets.

Chapter 13 highlight the potential aspects of ABC transporters in Alzheimer's disease treatment, while inadequate Aβ, which are physiologically assisted by the superfamily ABC transporters at the brain barrier, are essential in the progression of the disease.

Chapter 14 underline the importance for children with autism spectrum disorder to identify sleep profiles and to include various aspects of their symptom profiles in sleep deficiencies, resulting in new therapeutic strategies.

Chapter 15 focus on the cognitive impairment, executive dysfunction, and rehabilitation aspects of children and adults with autism spectrum disorder.

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Keywords

Acetyl cholinesterase inhibitors · Alzheimer's disease · Amyloid-β peptide · Apolipoproteins · ATP-binding cassette transporters · Autism spectrum disorder · Aβ precursor protein · Behavioral pathophysiology · Bioenergetics · Blood-brain barrier · Central nervous system · Childhood-onset schizophrenia · Cognitive behavior therapy · Complexity · Dementia · Dialectical behavior therapy · Dynamic programming · Environmental toxicity · Genetic predisposition · Hyperplasticity · Immune dysfunction · Immunotherapy · Insomnia disorder · Liposomes · lncRNAs · Medicinal herbs · Mercury · Microbiome · Mitochondrial dysfunction · Multiplex developmental disorder · Music therapy · Nanoparticles · Natural compounds · Neurodegeneration · NMDA receptor antagonist · Oxidative stress · Polyphenols · Sleep disorders · Prediction · Psychotic illness · RNA secondary structures · Schizophrenia · Social cognition · Speech therapy · Treating sleep

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1 Behavioral Pathophysiology and Psychological Implications for Sleep Disorder in Dementia

Rokeya Akter, Deepak Kaushik, Kuldeep Kumar, and Md. Habibur Rahman

Abstract

Dementia is considered rigorous neurodegenerative disarray, and it might be categorized addicted to numerous subtypes by dissimilar pathogenic reasons. Moreover, dementia is the typically second-hand expression for indicative and arithmetical physical 5 version main neurodegenerative disorders. These disorders characterized through functionally impairing refuse in individual or additional cognitive domains, like concentration, administrative role, reminiscence, or verbal statement, as strong-minded by equally the past and purpose deficits lying on bedside cognitive assessments or official neuropsychological trying. However, the burden of dementia is rising internationally. In the nonattendance of remedial action, defensive techniques to holdup or decrease succession of dementia are vital, relying on resting on the recognition of modifiable factors. The belongings of dementia lying on sleep are healthy documented; though, there is currently rising confirmation signifying bidirectional association connecting sleep pathologies with dementia. Equally, middle-aged and adult populations typically practice sleep-disordered breathing (SDB), deprived

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superiority sleep, and limits of sleep. It has been related to the amplified risk of dementia with cognitive refuse in an integer of observational reports, albeit disconnectedly. The mechanisms of sleep disorders might donate to neurodegeneration are various and comprise impacts of disjointed sleep on the permission of neurotoxins within SDB via the preservative property of irregular hypoxia beta-amyloid creation, hypoxic cell loss, neuroinflammation with injuring to intellectual vasculature. Neuroimaging modalities present vital opportunities to appreciate the connection between snooze pathologies with dementia risk in vivo, particularly in the severe preclinical stage of AD. In this chapter, we highlighted in dementia pathophysiology, the confirmation connecting sleep pathologies through dementia, insomnia disorder, management of sleep disorders in dementia, Treating sleep with breathing in dementia, and draw the improvement informative this possible pathophysiological connection to have eventuated the request of neuroimaging.

Keywords

Dementia · Behavioral pathophysiology · Psychological implications · Insomnia disorder · Cognitive behavioral · Poor sleep

1.1 Introduction

Behavioral and psychological symptoms of dementia (BPSD) are a heterogeneous collection of non-cognitive symptoms and behavior in people who have dementias. Evidence recommended sleep might manipulate heart biomarkers of Alzheimer's disease (AD) (Akter et al. 2021; Rahman et al. 2021). Complexity in declining sleep (Shokeir 2014), poor sleep eminence (Lucey et al. 2018), sleep beating (Lucey et al. 2017), excessive daytime drowsiness (Carvalho et al. 2018), and sleep muddled inhalation (Shim et al. 2017) was recommended to raise intellectual Aβ evidence in non-demented aged. Dementia is a top reason for disability and loss worldwide (Livingston et al. 2017). It recurrently unfavorably affects together prejudiced and goal index of sleep (Brzecka et al. 2018), counting sleep-disordered inhalation (Emamian et al. 2016). There is a mounting confirmation to sleep pathologies frequently lead to dementia analysis (Wennberg et al. 2017), suggesting that certain sleep changes might not merely be an indicator of enlarged risk but might straight donate to dementia pathogenesis, particularly dementia attributable to Alzheimer's disease. Apnea (Arya et al. 2021; Díaz et al. 2017) or disruptive sleep apnea condition (Hooghiemstra et al. 2016) was connected to superior levels of AD-associated neuronal damage biomarkers. Sleep eminence might even adapt to the defensive property of additional ecological factors like body work out (Brown et al. 2015) on brain Aβ statement. There are several mechanisms which use sleep abnormalities. The detection of such pathways is challenging, complemented more by the heterogeneity of sleep alters and calculations, the various pathological reasons as healthy as the manifold mediator and the confounding reasons for dementia which needed the accountability. Quality of sleep abnormalities reproduce preclinical

pathological alters in areas of the intelligence serious for an excellent sleep. Sleep troubles are widespread issues for adults (Dekker et al. 2019). Compromised sleep is connected with an inferior in general and sleep-related fitness position, which might guide to unhelpful individual and communal penalty (Del Campo et al. 2011). Individuals with sleep troubles account for superior levels of nervousness, unhappy mood, physical hurt and uneasiness, and cognitive deficiencies (Kyle et al. 2010). Insomnia might also be connected by long-term fitness penalty, counting augmented morbidity, respiratory illness, rheumatic illness, cardiovascular sickness, cerebrovascular circumstances, and diabetes. Besides, potential legion studies have originated that different sleep situations or parameters, like insomnia (Benedict et al. 2015), disruptive sleep apnea (Lutsey et al. 2018), sleep linked behaviors disarray (Yaffe et al. 2011), and altered sleep period (Westwood et al. 2017), might appreciably raise the risk of cognitive disorders between non-demented adults. In the past 2 existence, large amounts of legion studies have sprung up to discover the longitudinal incurring of sleep-connected exposures on events of cognitive disarray, which necessitates a resourceful methodical review. Generally, dementia is a scientific condition recognized through the expansion of cognitive mutilation of adequate harshness to crash a person's everyday function. It is also an analysis made following keeping out of reversible reasons. Nearly all dementias are progressive circumstances as bereavement is predictable and intended for which rejection healing action is obtainable (Livingston et al. 2017). Mild cognitive impairment (MCI) is a more syndrome analysis; within cognitive utility that is underneath that predictable for a period but is inadequate to collision everyday function. Among 39% of people through MCI resolve development to dementia. The commonness of dementia is powerfully connected to grow old, with about 1 in 10 peoples aged more than 65 years and 3 within 10 elderly 85 years plus over exaggerated (Ward and Pase 2019). Even though the convinced category of dementia happens in the middle time, 90% of belongings happen in persons elderly 65 existence and more than, income again? is termed late start dementia (Elahi and Miller 2017; Rahman et al. 2020a). Through populations mature, the quantity of dementia belongings internationally, predictable to be 47 million within 2015, is predicted to come near nearly 150 million through 2050 (Livingston et al. 2017). In this chapter, we highlighted in dementia pathophysiology, the confirmation connecting sleep pathologies through dementia, and sketch the advances informative this possible pathophysiological connection that might have eventuated as of the submission of neuroimaging.

1.2 Imaging Relation of Dementia with Alzheimer's Disease

The most common neurodegenerative disorders include dementia. Dementia. It increases memory loss, deterioration of thoughts, and dying ability to do everyday business. The primary common fundamental pathologies are: AD, vascular dementia (VaD), and frontal temporal dementia (Forette and Boller 1991; Kalaria et al. 2008; Rahman et al. 2021). Owing to their similarities in pathophysiology and other risk factors, it is difficult to differentiate AD from VaD (Erkinjuntti 2001; Rahman et al.

2020a; Roman 2001). Every pathology at different levels, ensuing in various patients by clean cerebrovascular sickness and clean AD instead of the range's limits (Erkinjuntti 2001; Roman 2001). Awaiting 2018, the worldwide figure of populace livelihood by dementia has been anticipated by about 50 million (Patterson et al. 2018), and the figure will triple through 2050. The aging of this resident has important implications for the emergence of dementia, subsequent impairment enlargement and dependency (Sousa et al. 2009, 2010). The information and quantity of aged people are quickly increasing in mounting countries like India, China, and America (Espenshade et al. 2003), and dementia completed the major giving to disability in these events (Sousa et al. 2009). It is well-known massive lumber for families, health-mind techniques, and the entire civilization to mind and props up patients through dementia (Etters et al. 2008). Internationally, the price of the disease is around a trillion US dollars per time, and the expenditure is expected twice to 2030. Unplanned sampling in the case of door-to-door populations is an alternative, reliable technology in these studies as it includes patients who are unable to seek fitness treatment (Pringsheim et al. 2014). Although, the diversification of showing tackle has to be documented as the main problem in the opinion of the factual occurrence (Mayston et al. 2014) and the difference in verbal communication and civilization, as healthy as literacy levels, create it an enormous fence to conquer. Furthermore, the extended latency epoch flanked by the start of neurodegenerative processes withal analysis of dementia happening poses an additional confront informative to what degree sleep alters indeed predate, and consequently might add to, neurodegenerative processes, as opposed to what degree slumber abnormalities reproduce preclinical pathological alters in areas of the intelligence dangerous for high-quality sleep.

1.3 Insomnia Disorder in Dementia

Sleep troubles are common concerns for the elderly (Young n.d.). Compromised sleep is associated with a minor in general and sleep-related fitness standing, leading to unhelpful individual and community consequences. Individuals through sleep problems state superior levels of nervousness, miserable humor, physical soreness and uneasiness, and cognitive deficiency. Long-term health effects such as increasing morbidity, lung disease, rheumatism, cardiovascular disease, brain conditions, and diabetes can also include insomnia.

1.4 Significant Role of Insomnia with Dementia

Although, insomnia comprises a grievance of reduced sleep, through associated significant daytime belongings, happening at the slightest 3 nights for each week for at least 3 months (Beck 1979). Universal, epidemiologic studies account for constant scientific insomnia disarray about 10–12% (Lichstein et al. 2013; More et al. 2013; Ohayon 2002). In one report, 74% of persons with insomnia sustained to

have sleeplessness a year afterward, and about 46% reported sleeplessness persisting in favor of more than 3 years (Morin et al. 2009a). Conventionally measured as 'secondary,' subsumed as symptoms of extra-scientific diagnoses inside mental well-being mind, the lately revised analytic and Statistical Manual of Mental Disorders, version 5 outlines the 'require for sovereign scientific notice of a slumber disorder' (American Psychiatric Association 2013). This is maintained by investigating representative not only to rates of cerebral and bodily health co-morbidity are elevated, but to pre-existing constant insomnia is a sovereign danger factor for the growth of gloominess (Baglioni et al. 2011), cardiovascular illness (Vgontzas et al. 2009a), and also category 2 diabetes (Vgontzas et al. 2009a, b). From the perspective of public well-being and happiness, sleep appears to exist an imperative subject that has been, up until now, renowned (Buysse 2014; Luyster et al. 2012).

1.5 Role of Pathophysiology in Dementia

There are numerous pathological reasons behind onset dementia. Correct classification needs neuropathological affirmation, although, in perform, judgment is based on syndromal observation. Around 2/3 of delayed dementia is due to AD (Rahman et al. 2020b; Uddin et al. 2020). This is pathologically well known through the development of cortically based extracellular beta-amyloid signs and neurofibrillary intracellular enclosures (Elahi and Miller 2017). The "amyloid cascade" principle of AD generally enhances the growth of beta-amyloid proteins. At the same time, the structure of cell membrane of small beta-amyloid peptide is inequitable. This is a higher protein such as amyloid precursor protein. Beta-amyloid cleavage with metabolism is damaged by a list of reasons that count heredity, partly unpredictable, although hypoxia and snooze may be significant. The excess beta-amyloid amassing can lead to an arrangement of Oligomers following these fibrils, following mats and finally extracellular plaques, which all serve to disrupt the position and relationship between neural cells. AD is next followed by expanding tau neurofibrillary tangles to spread during the intelligence happening intracellular injure, synaptic disability with neuronal cell loss, with contained hasty provocative processes accelerating injure. Jointly through structural neuroimaging events of neurodegeneration like as atrophy biomarkers strengthen the new National Institute of Aging and the Alzheimer's Association research structure that divides the attendance and phase of AD in vivo, recognizing to AD might be there in a preclinical phase biomarkers like as tau protein (Akter et al. 2021; Knopman et al. 2018). VaD is a different foremost donor behind beginning dementia. This might associate with big vessel stroke, which might be clinically "silent" brain planned lacunar infarction with little cerebral vessels' primary disease that might be calculated by the structural brain (Bos et al. 2018). Like AD, the VaD might also have an extended preclinical stage. Like dispersion tensor imaging (DTI), the latest structural imaging methods might allow the untimely test of the brain's pallid substance that might be distorted untimely in together vascular with AD pathologies (Bos et al. 2018). A combination of VaD with

AD pathologies is known and would seem to be phenotypically preservative (Arvanitakis et al. 2016).

1.6 Poor Sleep and Quality of Life Functioning

Characteristically, insomnia is connected with enlarged exhaustion, impaired labor output, condensed excellence of life with relationship approval, as healthy as augmented ill-health (Espie et al. 2012; Kyle et al. 2010; Roth and Ancoli-Israel 1999). Despite such confirmation of poor performance life form credited to deprived sleep and a necessary analytic principle for sleeplessness, there has been a moderately small investigation on life excellence. New astonishing known that the apparent collision on individual performance serves because of a significant driver of grievance and help-seeking performance rather than just apparent sleep defeat (Morin et al. 2006; Stepanski et al. 1989). In one big epidemiological report, four of the five mainly cited reasons for looking for a slumber discussion through a health expert were the morning penalty of exhaustion, mental suffering, physical uneasiness, and abridged work efficiency. Clinician information of enduring consultations, plus cross-sectional with prospective survey studies (Buysse et al. 2007; Levitt et al. 2004) additional display that persons through insomnia protest deficits in disposition, and cognitive power, joined through significant levels of nervousness, exhaustion, and bodily pain/uneasiness.

1.7 Insomnia Functioning with Cognitive Behavioral Therapy in Dementia

Cognitive-behavioral therapy (CBT) considered as the management of primary option for an importunate inadequate snooze (Espie et al. 2016; National Institutes of Health 2005), is a mental action intended to fracture the decoration of maladaptive thoughts and behavior to provide to uphold insomnia. CBT indicates various methods, counting a behavioral component joint through a cognitive with an instructive part. Meta-analyses point to CBT has reasonable to big and tough belongings on slumber excellence, sleep competence, sleep start latency plus wake-up time following sleep beginning (Mitchell et al. 2012; Trauer et al. 2015; Wu et al. 2015). Furthermore, about 60% of persons who be given CBT react to the action, and 39% attain reduction (Morin et al. 2009b). Rationally, effective action must lessen like impairments. Based on the confirmation that impaired sleep might be causally connected to condensed excellence of life domains, improving sleep should improve performance. There are a few beginning confirmations from minor analyses that CBT might yield widespread profits (Espie et al. 2001, 2007, 2008; Morin et al. 2009a), and still, a few primary data in little samples with CBT for sleeplessness might decrease depressive or nervousness symptoms (Manber et al. 2008; Pillai et al. 2015), but a sufficiently motorized, ultimate trial investigative useful health rank and well-being is extended unpaid.

1.8 The Role of Sleep in Dementia

It has elevated gratitude for the role of potentially adaptable dementia agents, such as high blood pressure, fatness, diabetes, sadness with low cognostic levels, and physical activity. These risk factors can be predicted jointly to contribute to over one-third of all traditional AD-related causes and to support the basis for many studies assessing multi-programming interventions in individuals. This background may be an unusually contemporary role of sleep pathologies in dementia. A number of resident studies with SDB propose (Ward and Pase 2019), low sleep excellence, extremely short or extended sleep before alters in slumber building (Pase et al. 2017) connect with higher risk dementia, counting dementia owing to equally AD with VaD. Although, these relations have not been time after time exposed. Besides, sleep changes might impact dementia risk through other pertinent mediators or connected factors, like obesity and diabetes. It is too hard to decide to what degree sleep alters are resultant as of preclinical neurodegenerative alters.

To be grateful for how sleep alters impact dementia pathogenesis, it is careful to appraise the contact dementia and MCI containing lying on sleep. People live through dementia are merely too well-known by alters in sleep to happen in dementia, like complexity through sleep start, distorted sleep/wake upcycles, disjointed sleep at night-time, extreme daylight sleepiness, and the augmented periods of daylight sleep (Musiek et al. 2018). Polysomnography reports explain improved sleep latency, abridged competence, augmented quantity of occasion exhausted in the lighter sleep events, and condensed time exhausted in sluggish-wave with fast eye group sleep in dementia. Comparable alters are also established in MCI, like in the society-based study. The fundamental sleep mechanisms that affect dementia may tell of a breach of neurodegenerative alterations by circadian beat of the brain and those concerned in the reserve of cortical stimulation, in particular circadian beats, changing sleep–wake-up cycles and a multiplicity of night-time arousals. Pet experiments showed that a stubborn sleep/wake-up cycle connects the Beta-amyloid accumulation (Roh et al. 2012). Tau protein collection takes place early on the hippocampus, a region essential to the development of non-RM slumber spindles with slow-gesticulation sleep, in the medial chronological lobe (Fjell et al. 2017). Cortical beta-amyloid accretion into the prefrontal cortex of medial media seems to harm the development of lenient oscillation of NREM (Mander et al. 2015). MCI dementia is also strongly linked to SDB. A meta-study of SDB in dementia recorded is approximately five times in stable older adults. MCI is related to the cognitive ordinary cognitive normal (CN), with a far superior apnea–hyperpnea directory in an elderly population Example of HypnoLaus (Haba-Rubio et al. 2017). This might be unbalanced ventilator manage ensuing beginning disjointed sleep, alter in the neuromuscular executive of the higher airway owing to degenerative alter the post middle gyrus (Joo et al. 2013) as like as upper airway power flaw, due to sarcopenia/bodily infirmity to regularly coexists with dementia. The pathological match-up has to establish to in AD, and tau protein accumulates untimely in the locus coeruleus, a section of the intelligence significant in inhalation directive and attentiveness (Fig. 1.1).

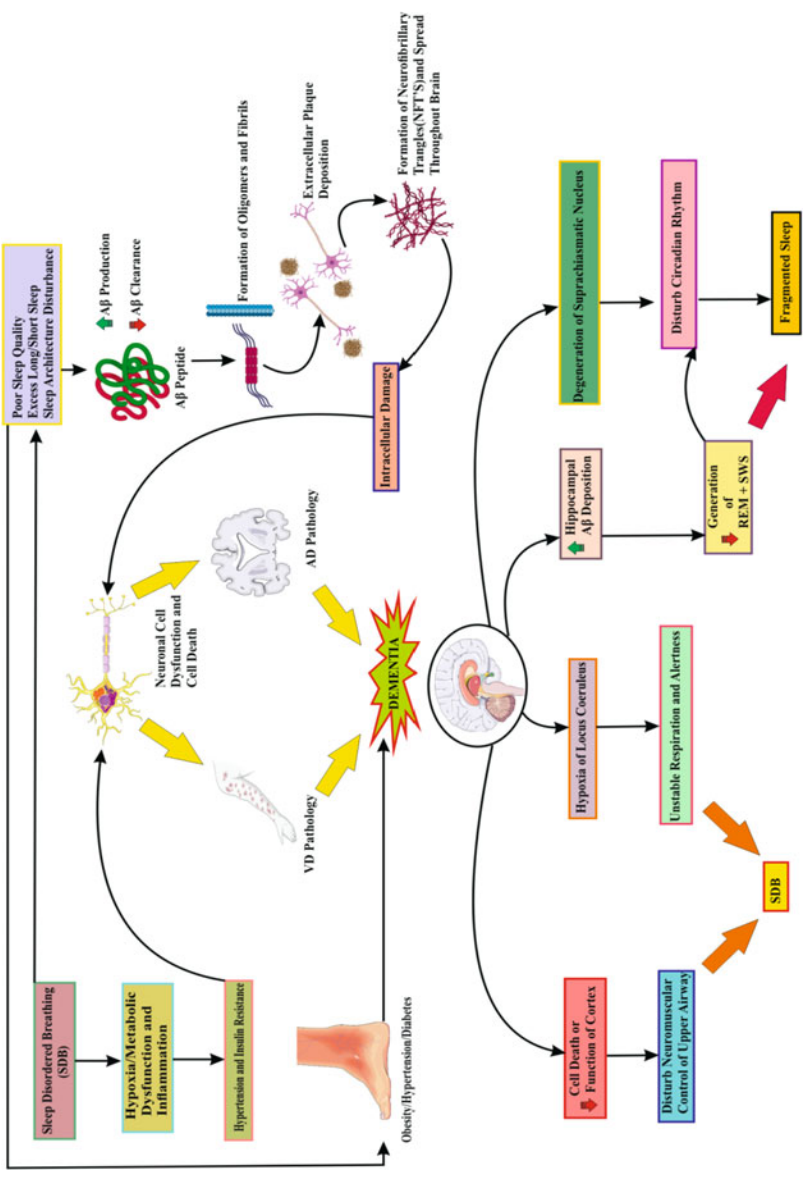

Fig. 1.1 Neuroimaging may reveal some of the pathways involved in sleep disorders that have a bidirectional relationship with neurodegeneration. Disjoined sleep may lead to condensed Aβ allowances, enabling the accumulation of toxic amyloid plaques to trigger AD pathology

1.9 Sleep Disorders Mechanism in Dementia Pathogenesis

Sleep play together healing and defensive actions in the brain and inequity might reasonably donate to neurodegeneration (Fig. 1.1). Several fundamental mechanisms are partially understood. For healing actions, sleep seems vital for the record of genes necessary for neural compartment casing and myelin honesty (Elvsåshagen et al. 2015), particularly in the pallid substance (Sexton et al. 2017; Takeuchi et al. 2018). Specific regions and functions of the intelligence in exacting might be more reliant on slumber for neural physical condition, such as preservation and reinstatement of hippocampus synaptic membranes (Van Someren et al. 2019). Sleep too appears vital for the intonation of synaptic relations, a procedure dangerous for knowledge and reminiscence (De Vivo et al. 2017). Crossways the era range, reports have exposed the significance of sleep on useful brain fitness events, particularly for the cognitive domains of reminiscence with concentration, as healthy as disposition with behavior (Scullin 2017). As a result, disturbed sleep can have reversible effects on cognitive utility, exacerbating dementia-related cognitive deficits, or contribute to minor neural cell loss and impairment that may be preservative to other neurodegenerative processes, lowering the threshold of pathological change required for dementia examination. Newly, pseudo-lymphatic coordination was discovered to give details on how the brain recover potentially neurotoxic squander (Iliff et al. 2012). This glymphatic structure has been exposed to be optimized throughout sleep (Xie et al. 2013). There is a preservative property in SDB. In addition to troublesome sleep, the periodic reductions and seizures through respiration help SDB guide irregular drops in oxygenation stages. Hypoxia itself might potentiate neural compartment loss with dysfunction, particularly inside the hippocampus, (Yuan et al. 2015), and has also been linked in mammal models through improved creation and condensed permission of beta-amyloid ("Leaf-nosed bat," 2009).

1.9.1 Consideration with the Management of Sleep Disorders in Dementia

Diagnosing sleep troubles in the populace through dementia might be complicated due to impaired reminiscence and short an imminent (Alzheimer's Association 2016; Roth 2012). For that reason, it is significant to meet together patients with caregivers (Urrestarazu and Iriarte 2016). Throughout these interviews, divan with wake-up times and bedtime routines must be reviewed. It thought to be renowned by sleep troubles in the populace through dementia are linked with lumber in caregivers of people through dementia, in exacting spousal caregivers (Rongve et al. 2010). Indeed, sleep troubles in dementia patients connecting to caregiver lumber have been established to be the main reason for the insertion populace through dementia in treatment homes (Pollak and Perlick 1991), identifying by treating slumber troubles in dementia might be vital to the happiness of patients and caregivers. We have encapsulated our suggestions in (Table 1.1) and meant for new particulars, see a new widespread review through Ooms and Ju (2016).

Table 1.1 Suggested treatments for dementia patients through sleep troubles

Sleep problem	Recommended pharmaceutical approach	Recommended non-pharmaceutical approach
Insomnia	Low dose (25–50 mg) trazodone; mirtazapine; melatonin	Bright light treatment; tumbling or withdraw caffeine with alcohol; dark and calm bedroom; not eating near bedtime; evade daytime sleeping; daytime bodily action
SDB	Think discontinuation of medications to might get worse SDB (e.g., benzodiazepines)	CPAP
Daytime sleepiness	Melatonin; altering present medication category with dosing	Daytime bodily movement
RBD	Melatonin; clonazepam	Eliminate potentially harmful substance from the bedroom; make barriers; evade antidepressants like caffeine and chocolate

Abbreviations: *CPAP* continuous positive airway pressure, *PD* Parkinson's disease, *RBD* rapid eye movement sleep behavior disorder, *SDB* sleep-disordered breathing

1.9.2 Daytime Sleepiness Treatment

Comparable to management for insomnia, melatonin has too exposed to get better daytime drowsiness and raise daytime motion (Brusco et al. 2000; Cohen-Mansfield et al. 2000; Dowling et al. 2008; Mishima et al. 2000). Daytime sleepiness might also be alleviated by altering the medication category with dosing (Urrestarazu and Iriarte 2016). Daytime sleepiness is general between people through dementia and is a particular predicament in PD. A new meta-analysis established that bodily activity might improve morning sleepiness, as healthy as numerous additional symptoms considered to be connected through sleep interruption in PD (Cusso et al. 2016). Confirmation from reports investigating pharmacological treatments' contact suggests with modafinil, and smaller amounts of caffeine with atomoxetine might improve too much daytime drowsiness in PD (Rodrigues et al. 2016). Overall, daytime drowsiness and night-time sleep troubles are regularly connected, with one problem exacerbating the new, so techniques aimed at referring problems might help lessen the new as glowing.

1.9.3 Treating Sleep with Breathing in Dementia

Continuous supportive airway stress therapy is often used to treat sleep-disordered breathing. Dementia patients with SDB seem to tolerate it at the same pace as non-demented SBD patients (Harmell et al. 2016) though, people with dementia through different neuropsychiatric syndromes might not accept continuous positive airway stress as well (AnChiu et al. 2008; Cooke et al. 2009). Two reports recommend to along with people among AD and SDB, and continuous positive airway stress use might help get better cognition, humor, and drowsiness (Ancoli-Israel

et al. 2008; Cooke et al. 2009). Continuous positive airway pressure has also been shown to lead to increases in hippocampal with cortical quantity, as well as blood oxygenation level dependent signals in the prefrontal cortex through subcortical areas (Archbold et al. 2009; Ayalon et al. 2006; Thomas et al. 2005; Zhang et al. 2011) which might potentially advance cognition.

1.9.4 Neuroimaging Studies in Dementia

Mainly significant proceed inconsiderate the relation among sleep disorders within scrupulous AD has been recognized through amyloid PET, known beta-amyloid lumber is prognostic of event dementia are shown in Table 1.2 (Elahi and Miller 2017). A study of 20 healthy men and women, with an average age of 40, who recorded their normal sleep cycle and then underwent sleep deficiency testing, is one of the most notable findings. The two were connected by baseline beta-amyloid timber, and the latter showed an improvement in all night beta-amyloid levels in the thalamus and hippocampus (Shokri-Kojori et al. 2018). Unhelpful health results connected to little sleep were too reported in an elder assembly of 70 men with women by a middle-age of about 76. Identity reported slight sleep was connected cross-sectionally through elevated beta-amyloid in the presumes with largely cortical freight, (Spira et al. 2013). However, no similar connections were found in three additional similarly sized irritated sectional studies analyzing sleep time in cohorts by a mean period of 62–76 life (Branger et al. 2016; Brown et al. 2016; Sprecher et al. 2015). In multiple studies elder populations, self-studied sleep dominance has to be originated to be linked cross-sectionally across global and local cortical beta-amyloid (Spira et al. 2013; Sprecher et al. 2015) particularly in connection by increased sleep latency (Branger et al. 2016) as like as linked by sleep construction alter as captured via PSG17 with actigraphy.

1.10 Conclusion with the Future Direction

The connection between sleep and dementia is complex and most likely bidirectional. Snoozes, as well as dementia, are associated with a number of customs. Sleep disturbances can be caused by a brain pathology called fundamental dementia. Via co-occurring sleep turbulence, sleep commotion may contribute to the improvement of dementia, and dementia may lead to a more rapid decline. The majority of the studies that have been related cross-sectional and warned on sleep as a risk factor for Alzheimer's disease (Cooke et al. 2006; Cricco et al. 2001; Lobo et al. 2008; Osorio et al. 2011; Talarico et al. 2013). Identifying by treating troubled sleep in people through dementia might improve multiple results, counting dementia route and caregiver lumber (Etters et al. 2008; Pollak and Perlick 1991). Sleep is an adaptable action. It is also a vital possible aim for involvement in cognitive refusal with dementia. Sleep as early on as in the prime of life might raise the hazard of dementia; this might have important implications for AD avoidance. Sleep, like other risk

Table 1.2 Beta-amyloid lumber is prognostic of event dementia

Study	Population	Design	Sleep measure	Confounders	Outcomes
Sleep quality					
Spira et al. (2013)	$n = 70$, F = 47% Age = 76 CN + MCI + D	Cross-sectional	Self-report WHIRS	Age/sex/race/BMI CVD/lung dis/depression Sleep meds/APOE4	↓ Sleep quality →
Spira (2014)	$n = 8$ CN, age 69 $n = 5$ MCI, age 75	Cross-sectional	PSG TST, AI, WASO	–	↑ Aβ in presumes
Mander et al. (2015)	$n = 26$, F = 69% Age = 75, CN	Cross-sectional	PSG EEG NREM and SWS	Age, sex Gray matter volume	↑ Aβ prefrontal cortex→
Branger et al. (2016)	$n = 51$, F = 55% Age = 64, CN	Cross-sectional	Self-report (PSQI)	Age/depression/anxiety/BMI/APOE4	↑ Sleep latency → ↑ Aβ
Sleep duration					
Sprecher et al. (2015)	$n = 98$, F = 67% Age = 62, CN	Cross-sectional	Self-report (MOS)	Age/sex/BMI/ Fam Hx AD/APOE4	No assoc
Branger et al. (2016)	$n = 51$, F = 55% Age = 64, CN	Cross-sectional	Self-report (PSQI)	Age/depression/anxiety/BMI/APOE4	No assoc
Daytime sleepiness					
Sprecher et al. (2015)	$n = 98$, F = 67% Age = 62, CN	Cross-sectional	Self-report (MOS and ESS)	Age/sex/BMI/ Fam Hx AD/APOE4	Sleepiness on MOS (but not ESS)→↑ Aβ
Carvalho et al. (2018)	$n = 283$, F = 28%	Longitudinal 2 years	Self-report (ESS)	Age/sex/Educ/PA/obesity/HT/DM/ Chol/depression/APOE4	EDS→ ↑ accumulation of Aβ

	Age = 77, CN + MCI				
Sleep-disordered breathing					
Spira (2014)	*n* = 8 CN, age 69 *n* = 5 MCI, age 75	Cross-sectional	PSG: AHI, TST AI, WASO	–	In MCI, ↑ AHI → ↑ Aβ global, precuneus
Elias (2018)	*n* = 42 w OSA, CN 77 controls Age = 68	Cross-sectional	OSA + CPAP use/PSG	Age/Educ/vascular APOE4/BMI	No assoc. of Aβ or tau in adjusted models with OSA or CPAP

Abbreviations: *Aβ* beta-amyloid, *AD* Alzheimer's disease, *AHI* apnea–hypopnea index, *AI* arousal index, *APOE4* apolipoprotein E4; assoc., association, *BMI* body mass index, *Chol* cholesterol, *CN* cognitively normal, *CPAP* continuous positive airway pressure, *CVD* cardiovascular disease, *D* dementia, *DIS* difficulty initiating sleep, *DM* diabetes mellitus, *EDS* excessive daytime sleepiness, *Educ* education, *EEG* electroencephalogram, *ESS* Epworth Sleepiness Scale, *ETOH* alcohol use, *F* female, *Fam Hx AD* family history of AD, *HT* hypertension, *lung dis* lung disease, *MCI* mild cognitive impairment, *MOS* Medical Outcomes Sleep Scale, *n* number, *NREM* non-rapid eye movement, *OSA* obstructive sleep apnea, *PA* physical activity, *PET* positron emission technology, *PSG* polysomnography, *PSQI* Pittsburgh Sleep Quality Index, *SD* sleep deprivation, *SWS* slow-wave sleep, *TST* total sleep time, *WASO* wake after sleep onset, *WHIRS* Women's Health Initiative Insomnia Rating Sca

factors for Alzheimer's disease, will need to be challenged in midlife. However, more investigation in this field is required. Affecting ahead, sleep investigation can decide trajectories of dementia, get a better patient prediction, and decrease the threat of deprived scientific consequences, as well as dementia oneself.

Conflict of Interest All the authors declare that they have no conflict of interest.

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Mitochondrial Dysfunction: A Key Player in the Pathogenesis of Autism Spectrum Disorders and Alzheimer's Disease

2

Aisha Farhana and Yusuf Saleem Khan

Abstract

Increasing evidence has pinpointed that loss of mitochondrial function or regulation is a critical player toward the pathogenesis of various metabolic, neurodevelopmental, and neurodegenerative disorders, including autism spectrum disorders (ASD) and Alzheimer's disease (AD). The lacuna in understanding these diseases' underlying biology is that pathology develops through the interaction of various biological pathways rather than a defined mechanism. Mitochondria are dynamic organelles that perform diverse functions, including cellular energy production, calcium homeostasis, apoptosis, and innate immune regulation. Hence, mitochondria integrate various cellular pathways, and any exogenous or endogenous perturbation may result in their dysfunction. Herein, we explore the latest research insights that have evolved our understanding of ASD and AD pathogenesis with the perspective of mitochondrial dysregulation as the underlying phenomenon. We discuss the pathological relevance of cause and effect of mitochondrial dysregulation, such as increased reactive oxygen species (ROS) production, mitochondrial DNA damage, aberrant immune responses, impaired energy metabolism, and altered gut microbiome in the etiology of ASD and AD. Being at the center stage, mitochondria have emerged as a novel target with considerable therapeutic potential, which can be exploited to delay, manage, or treat ASD, AD, and other neurological disorders. We also discuss the novel therapeutic options such as H_2S therapy, dynamic microbiome modulation, ketogenic diet, and cofactor therapy that are emerging as a plausible

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treatment regimen and have shown favorable outcomes in initial studies. Hence, this article summarizes the current understanding of the functional and structural disturbances in the mitochondria that lead to ASD and AD and could be harnessed for better diagnostic and prognostic outcomes.

Keywords

Mitochondrial dysfunction · Autism spectrum disorders · Alzheimer's disease · Oxidative stress · Microbiome · Bioenergetics · Immune dysfunction

2.1 Introduction

Mitochondria are a double membrane organelle of approximately 0.75–3 μm^2 size present in all cells of the eukaryotes and almost all prokaryotes. They act as the powerhouse of cells by producing energy in the form of adenosine triphosphate (ATP), which is required for cellular functions. Other functions of mitochondria include cellular differentiation, signaling, cell growth, death, and cell-cycle regulation. Mitochondrial structural and functional abnormalities have been demonstrated as a common shared mechanism across multiple neurodegenerative disorders that include diseases/syndromes such as cardiovascular disease; diabetes; schizophrenia; myopathy; stroke; endocrinopathy; bipolar disorder; chronic fatigue syndrome; Pearson syndrome; dementia; Kearns-Sayre syndrome; Parkinson's disease; Leber's hereditary optic neuropathy; Barth syndrome; retinitis pigmentosa; Alzheimer's; Friedreich's ataxia; mitochondrial encephalopathy, lactic acidosis, and stroke (MELAS) syndrome; Wilson's disease; progressive external ophthalmoplegia; myoclonic epilepsy with ragged red fibers (MERRF); hereditary spastic paraplegia; etc. But most often, it presents itself in the form of neurological diseases such as ASD and AD. Present epidemiological data confirms that almost 5–80% of children affected by ASD show mitochondrial dysfunction compared to only 0.1% among the general population (Rose et al. 2012; Bayer 2015). Pathophysiological studies have shown a distinct connection between mitochondria and AD; however, an exact epidemiological data is not available thus far.

ASD represents a group of confounding diseases that include autism, Asperger's syndrome, and pervasive developmental disorders. ASD is marked by developmental and neurological syndromes that lead to impaired social communication abilities and repetitive behavior. ASD symptoms start to manifest during early childhood and last throughout the lifetime. On the other hand, AD is a progressive degradation of brain cells, usually in the elderly, leading to dementia, which affects a person's social abilities. Though both disorders are at the two ends of the age spectrum, they have common clinical manifestations such as language impairment, a problem in executing functions, dementia, and motor disability (Khan et al. 2016). Understanding ASD and AD from a biological perspective becomes complex due to its diagnosis solely through behavioral criteria directed by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), which keeps being revised based on

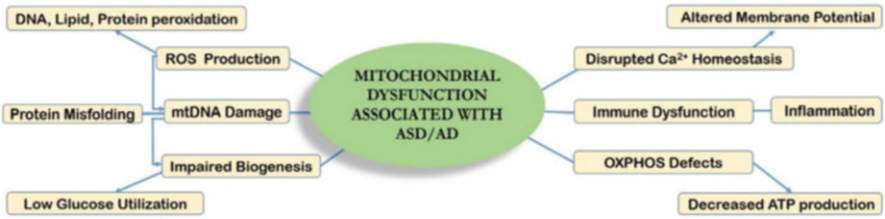

Fig. 2.1 The effectors of mitochondrial dysfunction associated with ASD and AD

identifying more contemporary patients' patterns. The identification of ASD and AD through behavioral benchmarks is partly due to an insufficient understanding of the biological processes and the non-availability of quantitative biomarkers for these diseases. The cavities in understanding these diseases' biology is that the pathology develops through a complex interaction of several biological pathways rather than a defined mechanism. It involves biological components as diverse as bioenergetics, epigenetics, and genetics, besides having environmental effectors.

The pathologies observed in ASD and AD, such as toxic accumulation of protein aggregates in AD, and increased white matter neurons together with a substantial decrease in the GABAergic cerebellar Purkinje cells in ASD, can be due to mutation, rearrangements, or point mutations in mitochondrial DNA (mtDNA). Recent researches indicate that diseases such as Parkinson's disease, AD, Rett syndrome, and ASD plausibly share a common mechanism of mitochondrial dysfunction leading to disease progression (Frye 2020). Over the last few decades, despite a compelling problem of underdiagnosis, there has been a surge in the prevalence of ASD worldwide (Chiarotti and Venerosi 2020; Maenner et al. 2020). Many studies indicate that mitochondrial dysfunction may have an essential role in the development of ASD. It is also reinforced by the evidence that several comorbidities that develop due to mitochondrial defect such as epilepsy, sleep apnea, gastrointestinal, and immune dysfunction share an association with ASD. Mitochondria are sensitive organelles susceptible to endogenous alterations such as iatrogenic medications, toxicants, immune activation, and metabolic disruption besides the exogenous environment. The general effectors for mitochondrial dysfunction that facilitate progress toward AD and ASD are illustrated in Fig. 2.1. Many of these stressors have also been demonstrated in the etiology of ASD. Hence, there seems a clear link between these two disorders, which points to a possible shared etiological mechanism.

Furthermore, AD also has multiple etiological factors, and aging is considered a significant risk factor. Most studies on AD have focused on τ (tau) and amyloid-beta (amyloid-β) pathology as underlying factors. Some studies have demonstrated that τ pathology contributes to mitochondrial dysfunction leading to neurodegeneration. Amyloid-β protein has been shown to accumulate in the mitochondrial matrix hampering its function, such as failure of energy metabolism, generation of reactive oxygen species (ROS), and permeability transition pore (PTP) formation. Hence, it could be conjectured that brain metabolism in AD may be deranged due to altered

mitochondrial functionality. This hypothesis had opened up new frontiers to explore alterations in mitochondrial bioenergetics as a possible cause of ASD, AD, and associated pathologies. Recent research studies have provided insight into novel metabolic targets to treat or prevent ASD and AD pathogenesis.

In this article, we discuss the latest findings that support that mitochondrial dysfunction and functional and structural abnormalities in mtDNA are the central mechanisms toward the pathogenesis of ASD and AD. We will also analyze the association of ASD and AD with respective co-occurring medical conditions in the light of mitochondrial dysfunction at the center stage. The review will also focus on understanding the advancement in the therapeutic approaches used for remodeling and enhancing mitochondrial functions, leading toward novel treatment methodologies for treating or managing ASD and AD.

2.2 Increased Oxidative Stress Linked to Mitochondrial Dysfunction in ASD and AD

The regulation of cellular survival, orchestration of biosynthetic metabolic pathways, and ROS signaling are the canonical functions of mitochondria. These organelles are integral to supporting the energy requirement of our body's metabolic processes during the resting, active, and stressed state. They populate the cells of the body and harbor their mtDNA (mitochondrial DNA). Besides catabolizing glucose and oxidizing fatty acids to generate ATP, mitochondria play a distinct role in forming reactive oxygen species (ROS), calcium signaling and homeostasis, and the regulation of programmed cell death (Malek et al. 2018).

The accumulation of τ-protein and amyloid-β plaques is a pathological hallmark of AD that consequently progresses toward developing the disease. On the other hand, behavioral challenges mark the identification of ASD. Studies spanning the past few decades have determined that many factors, including biological, environmental, lifestyle, epigenetics, and genetics, influence the development of the two diseases. However, the mechanism of pathogenesis remains elusive. Recent studies have furnished distinctive insights that underscore mitochondrial dysfunction as an early event in ASD and AD pathogenesis (Rossignol and Frye 2012; Frye 2020). Oxidative stress plays a pivotal role in linking mitochondrial dysfunction and neurological disorders. Imbalances in the cellular milieu rendered through the presence of pro-oxidant metabolites, activated immune cells, toxicants, etc. subsequently lead to mitochondrial dysfunction.

The notion that mitochondrial abnormalities may be the cause of ASD came up in 1985, with the observation of lactic acidosis in children with ASD. Presently, ASD is quite common among children and is noted to be affected by different triggering etiologies, one of them being physiological abnormalities of mitochondrial dysfunction widely ranging from 5 to 80% (Rose et al. 2012). Similarly, metabolic changes and increased ROS production in AD brains underscore mitochondrial abnormalities at their nexus. With the advent of more recent techniques, considerable evidence has now accumulated that pinpoints oxidative stress, and calcium homeostasis

alterations precede the formation of pathological identifiers in AD, such as plaques and tangles in the brain (Von Bernhardi and Eugenín 2012).

The mitochondrial electron transport chain (ETC) is the underlying source of ROS production. ROS serves as a signaling molecule under normal concentrations, modulating numerous physiological reactions, including the ETC, ion transport, and neurotransmitter receptors. If ROS production exceeds the physiological system's buffering capacity, it manifests in the form of oxidative stress. The primary cause of oxidative stress is the abnormality in ETC. Increased ROS in the AD brains, as well as a region-specific reduction in the blood flow and oxygen utilization, provide ample evidence implicating compromised mitochondrial physiology in the development and progression of the disease (Bonda et al. 2014). Unregulated ROS production causes damage to cellular lipid, protein, and DNA, leading to derangement in the metabolic processes or development of anatomical lesions. The brain regions that were found to be most vulnerable to high ROS were the frontal, parietal, and temporal lobes. These areas overlap the areas that are found to be affected in AD patients (Wang et al. 2006).

Higher ROS levels induce ASD cascade, which posits mitochondrial abnormalities as the critical origin of neurodevelopmental impairment in ASD. However, these deficits in the mitochondria's ETC complex activity are distinct from the abnormalities observed in classical mitochondrial diseases. Studies have identified higher ETC complex IV, III, and I activity in ASD animal models and patients (Frye and Naviaux 2011; Delhey et al. 2017; Valiente-Pallejà et al. 2018). Others have linked reduced antioxidant capacity and increased ROS levels at the systemic level in ASD. Molecules of oxidative stress have been shown in the brains of ASD patients and also in their parents (Ohja et al. 2018). Another study demonstrated impairments in the glutathione redox balanced in cerebella and temporal cortices of autistic patients (Rose et al. 2012). Transcriptional profiling of 84 genes of oxidative stress machinery identified a signature pattern of eight genes, namely, glutamate-cysteine ligase modifier (*GCLM*), superoxide dismutase 2 (*SOD2*), neutrophil cytosol factor 2 (*NCF2*), prions (*PRNP*), prostaglandin-endoperoxide synthase 2 (*PTGS2*), thioredoxin (*TXN*), and ferritin heavy chain (*FTH1*), involved in ROS metabolism which were downregulated in autistic individuals (Bolotta et al. 2018). Further, RBC damage through ROS that causes altered RBC shape and morphology has been a significant feature in autistic patients (Bolotta et al. 2018).

Interestingly, immune dysfunction identified as one of the pathological features of ASD has a close link with oxidative free radicals accumulation. Altered redox balance either in the prenatal or postnatal period is associated with immunological activation, which increases the risk of autism in children. Though prenatal immune dysregulation is not clearly understood, exposure to unhealthy postnatal environments is linked to a distinct immune dysregulation pattern, endogenous autoantibodies, and inflammation observed in autistic patients. Mitochondrial functional abnormalities can initiate specific stress signals leading to an aberrant immune response. Nonetheless, a meticulous approach toward understanding the molecular pathways that trigger inflammasome cascade resulting from mitochondrial

dysfunction needs further research (Chen et al. 2018). A thorough understanding of metabolic circuitry that underscores mitochondrial dysfunction in ASD and AD may facilitate novel treatment strategies.

2.3 Mitochondrial DNA Damage Promotes the Development of ASD and AD

Mitochondria are present in every cell at varying numbers depending upon the difference in tissue origin. Cells of tissues with greater metabolic demands like the brain, cardiac, and skeletal muscle tissues have many mitochondria. Each mitochondrion harbors many copies of mtDNA. Moreover, mitochondrial genomes have 10–20-fold high mutation rates compared to nuclear DNA, which renders them inherently heteroplasmic (Stein and Sia 2017). Studies have reported that mitochondria have a skewed concentration of nucleotides that compromise mtDNA polymerase subunit gamma (PolG) enzyme fidelity, corroborating higher mutation rates in mitochondrial DNA. Consequently, these mutations accumulate more in tissue with higher metabolic activity, such as the brain, leading to more pronounced phenotypes.

Additionally, mitochondria are subjected to oxidative stress due to their respiration function, which can induce oxidative lesions in their genome (Sharma and Sampath 2019). ASD and AD, besides other neurodegenerative diseases, have higher ROS concentrations, and reports have demonstrated its association with the deletion of mtDNA. Diminished mitochondrial genome integrity has now been understood to predispose early- and late-onset metabolic diseases such as ASD, Parkinson's disease, and Alzheimer's disease.

mtDNA mutations occur across polypeptide mutations, rRNA and tRNA mutations, rearrangement mutations, and mutations in the regulatory region affecting mtDNA replication and transcription. A study on ASD children indicated that around 28.6% of ASD subjects displayed mutations commonly associated with mitochondrial disorders, such as the presence of low mtDNA content and putative pathogenic mtDNA mutations (Varga et al. 2018). mtDNA haplogroup differences can contribute to the modulation of the ASD risk. A cohort study of 1624 patients with ASD identified many mtDNA haplogroups across different clusters in ASD. Hence, mitochondrial haplogroups associated functional variants could be a risk factor for developing ASD (Chalkia et al. 2017). Using databases of mtDNA sequence and variation (comprehensive MITOMAP, A Human Mitochondrial Genome Database initiative), many mutations in mtDNA have been identified that are linked to pathologies and comorbidities associated with ASD and AD (Sharma and Sampath 2019). Several genetic anomalies are related to mitochondrial defects in ASD, including mitochondrial DNA mutations and deletions and chromosomal abnormalities. These abnormalities have been identified in buccal cells and cells of the immune system, fibroblasts, gastrointestinal tissue, and muscle, besides in the brain tissue of patients with ASD.

Studies on AD brains have shown reduced mtDNA content and mass, increased fragmentation of mtDNA, deletion, and apoptotic cell loss, associated with elevated free radicals linked with a reduced cyclooxygenase (COX) level. In a downstream signaling cascade that perpetrates with mitochondrial stress, cell apoptosis is triggered. These innate immune mechanisms are susceptible to nuclear and mtDNA and any other type of DNA from the phagolysosomal compartment. The presence of apoptotic vesicles in the blood from ASD patients, which in turn contain a considerable concentration of mtDNA, is plausibly recognized as an innate pathogen in ASD. These vesicles enter the microglia of ASD patients through blood and lymphatic systems and triggering an immune response (Pangrazzi et al. 2020). Many studies have also observed sporadic mtDNA deletions in brain tissues obtained after the postmortem of late-onset AD patients. In a study, $mtDNA_{\Delta 4977}$ showed a 15-fold hike in its occurrence in AD subjects' cortical neurons (Phillips et al. 2014). Visible chromosomal lesions and slight copy number variants at 16p11, an inverted duplication on one of the domains of chromosome 15q11-q13, are also commonly observed in 10–20% of ASD cases (Cook Jr et al. 1997; Qureshi et al. 2014).

2.4 Calcium Homeostasis Imbalance Perpetrates Mitochondrial Dysfunction in ASD and AD

The function of mitochondria in regulating and buffering cytoplasmic Ca^{2+} (calcium ion) manifests as a central player in normal neurotransmission, neuronal plasticity, gene transcription regulation, and excitotoxicity (Celsi et al. 2009). Different studies have cited the function of mitochondria in Ca^{2+} buffering impairment in the aging brain and AD (Camandola and Mattson 2011). Disturbances in the Ca^{2+} homeostasis are closely connected with mitochondrial permeability transitions potentiated by high ROS generation, elevated phosphate concentrations, and ATP depletion. This eventually leads to the release of pro-apoptotic factors and cell death (Toglia and Ullah 2016; Granatiero et al. 2019). Predominantly, the function of most of the ions is limited to electrical conduction at the cell membrane. However, calcium additionally integrates signaling to cellular transcriptional, translational, metabolic, and biochemical events. The intrinsic function of calcium as a second messenger arbitrates diverse cellular processes through spatial and temporal alteration in concentration (Berridge et al. 2000). This function is carried out by a multitude of calcium-binding proteins, transporters, and voltage-dependent ligand-gated ion channels. Since calcium plays a ubiquitous role in cell physiology, any regulatory defects in the calcium signaling pathway can disrupt neurological function as demonstrated by several pathological conditions, including ASD (Nguyen et al. 2018). Derangement in calcium signaling potentially causes many abnormalities associated with ASD pathogenesis, such as mitochondrial function defects, neurotransmitter signaling, and synaptic plasticity. Mechanistic variants have been identified in calcium signaling pathways related to the endoplasmic reticulum

(ER) and mitochondrial organelle dysfunction in ASD and AD. Though organelles are inherent to all cells throughout the body, the central nervous system (CNS) is profoundly affected by organellar diseases (Nguyen et al. 2018). Some genetic studies have also identified ion channel gene mutations in ASD subjects, suggesting it to be a channelopathy and a plausible reason for associated comorbidities (Noebels 2017).

Cognitive functions such as memory, neuron excitability, synaptic plasticity, axon growth, the release of neurotransmitter, and precise modulation of calcium gradients are regulated through intracellular calcium homeostasis (Wen-hong et al. 1998; Hernández-López et al. 2000; Neher and Sakaba 2008). Nerve stimulation is achieved by increasing cytosolic calcium from a resting concentration of ~100 nM by mobilizing calcium from intracellular ER stores or extracellular milieu. Mitochondria play a pivotal role during this signal transduction process by immediately sequestering Ca^{2+} through its calcium uniporter. Hence, the extracellular signal impulse is swiftly propagated through a tightly regulated mitochondrial process (Giorgi et al. 2012). Mutations in mtDNA affect calcium homeostasis, such as reduced Ca^{2+} sequestration, which consequently disturb ETC, mitochondrial membrane potential, and ATP production. ATP production is reduced due to the inability of Kreb's cycle enzymes to function in the absence of calcium. Positive feedback is generated with subsequent loss of ATP synthesis, which affects overall cell physiology. Besides, Ca^{2+} homeostasis derangement can also lead to intracellular Ca^{2+} overload within the mitochondria. In AD, the accumulation of amyloid-β facilitates ROS generation, which causes the accumulation of Ca^{2+} and PTP opening in mitochondria (Giorgi et al. 2012). Vitamin D is a key modulator of calcium homeostasis, which functions through its nuclear receptor, thereby controlling gene expression. It plays a crucial role in cellular proliferation and fine-tuning voltage-gated calcium channels. Furthermore, mitochondria are imperative in producing the active form of vitamin D, D3 (1α,25-dihydroxyvitamin-D3). The deficiency of D_3 during fetal life is strongly linked with the pathogenesis of ASD (Vinkhuyzen et al. 2017).

2.5 Neuronal Mitochondrial Dysbiogenesis Underlies the Development of ASD and AD

Many studies have demonstrated that mitochondrial biogenesis is fundamental to neuronal growth. Cellular pathways that are functional during neuronal development also promote mitochondrial biogenesis to arbitrate developing neurons' energy requirements. Mitochondrial biogenesis is regulated through a concerted mechanism manifested through crosstalk between mitochondrial and genomic DNA counterparts. Mitochondria proliferate and constantly fuse as a part of healthy cellular mechanisms and respond to enhanced energy needs, oxidative stress, and disease conditions. Mitochondrial biogenesis is controlled through checkpoints

during transcription, translation, and post-translation. This process is activated by peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) (Jones et al. 2012). Further, sequential activation of nuclear respiratory factor-1 and nuclear respiratory factors-2 (NRF-1 and NRF-2) transcription factors leads to mitochondrial biogenesis. These newly formed mitochondria are integrated into the mitochondrial metabolic machinery, while the ones that are nonfunctional or damaged or demonstrate possible membrane disruption are tagged for degradation and removal. The removal of damaged mitochondria follows an autophagy-dependent mechanism called mitophagy (Lou et al. 2020).

Additionally, mitochondrial dynamics are regulated through fusion and fission processes, which counteract cellular damage by complementing cellular components, besides removing damaged mitochondria through autophagy. The mitochondrial biogenetic pathways functional through NRF 1, NRF 2, PGC-1α, etc. are demonstrated to be impaired in neurological diseases such as ASD and AD. A number of mitochondria and biochemical mediators such as NRF 1, NRF 2, and mitochondrial transcription factor A (TFAM) and PGC-1α are shown to be decreased in the hippocampus of AD brains, which diminish AMP-activated protein kinase (AMPK)-induced neuronal growth. Disturbed mitochondrial biogenesis, demonstrated by altered expression of mitochondrial fission (Fis1 and Drp1) and fusion (Mfn1/2 and Opa1) proteins and in the temporal cortex, indicated its relation to differences in the morphology and function of mitochondria in ASD (Tang et al. 2013). Many studies have correlated this deranged biogenesis potential of mitochondria to the disruption of neuronal plasticity and compromised cellular resilience. This process is demonstrated to eventually regulate psychotic disorders regularly observed in psychiatric comorbidities (Quiroz et al. 2008).

Another feature of mitochondrial biogenesis is an interconnected network of proteases and chaperones that maintains the quality of proteins and remove damaged proteins from the mitochondrial compartment (Folisi 2015). During homeostasis, mitochondrial chaperons facilitate protein folding and translocation, while proteases degrade and remove misfolded and damaged proteins from the mitochondria. Impaired chaperons and proteases consequently lead to the accumulation of protein aggregates, such as τ-protein and amyloid-β in AD, which ensues in the form of mitochondrial dysfunction (Ruan et al. 2013; Deepa et al. 2016). Notably, genetic mutations could cause impaired functions of mitochondrial chaperones and proteases and are extensively demonstrated to precipitate severe neurological diseases (Martinelli and Rugarli 2010; Goo et al. 2013; Strauss et al. 2015). Though few studies have linked the impaired function of proteases and chaperons with AD, others have shown their upregulation to be a priming episode in amyloid progression and τ-pathology in AD (Beck et al. 2016; Sorrentino et al. 2017). Similarly, few researchers have identified impaired inner membrane protease polymorphic forms of *IMMP2L* in ASD. Recently, the identification of protease malfunction and its reciprocal effect in the development of ASD have also gained momentum.

2.6 Impaired Mitochondrial Energy Metabolism Propels the Development of AD and ASD

Brain function is a composite of neuronal and glial cell function and synaptic efficiency. Healthy neuronal function demand higher energy needs, and hence numerous mitochondria are present in the brain cells (Picard and McEwen 2014). The mitochondria carry out their primary function to synthesize ATP. Coherence with other cellular organelles provides buffering machinery that regulates calcium levels during nerve impulses and signal transduction. Besides, they are instrumental in the biosynthesis of heme and iron-sulfur (Fe-S) clusters required to synthesize presynaptic neuronal transmitters in synapses (Lin and Beal 2006). Hence, it is discernible that disruption of mitochondrial functions is likely to cause nervous system abnormalities leading to neurodegenerative or neurodevelopmental disorders (Alexiou et al. 2018).

The brain is one of the highest energy-consuming organs, which approximately uses 25% of total energy in the resting state. Hence, a deficit in the energy fuel supply, such as the availability of glucose, or metabolic machinery like mitochondrial dysfunction, negatively impacts brain function. Neurons highly depend on oxidative phosphorylation as a source of energy, which renders them susceptible to mitochondrial dysfunction (Cardoso et al. 2016. Studies using fluorodeoxyglucose positron emission tomography (FDG- PET) have identified low glucose metabolic rates in AD patients, especially in the posterior cingulate, temporal, and parietal lobes and the hippocampus (Kapogiannis and Mattson 2011). These regions are dedicated to cognition and memory, and hence defects in energy metabolism could be a proximate source of pathologies in neurological disorders such as AD and ASD. The hypometabolism of glucose in the AD brain is compensated by shifting to amino acid and lipids as energy sources (Toledo et al. 2017). Metabolomics and lipidomic studies have identified at least six central metabolic pathways, including glycerophospholipid and aspartate metabolism in human autopsy samples to be defective.

Similarly, essential amino acids, branched-chain amino acids (BCAAs), polyamine metabolism, and serotonin pathways in the APPswe/PS1deltaE9 double transgenic AD mouse model were found to be altered. Though these studies provide a direct link with AD, not all of these metabolic findings were replicated (Casanova et al. 2016; Pan et al. 2016). Presently, molecular networks, viz., systems biology approach, have identified metabolic connections in varied metabolic pathways, highlighting the dysregulation of biochemical reactions at different disease progression stages (Santiago and Potashkin 2014). This approach provides distinct mechanistic insight into complex diseases such as AD and ASD, which stem from changes in multiple genes, proteins, and metabolites.

Metabolites such as glutamate and glycolytic intermediates, lactate, and pyruvate were observed to be increased. In contrast, carnitine, the fatty acid carrier from the cytosol to the mitochondria, and glutathione were demonstrated to be lower than expected in the serum of ASD and AD patients (Shimmura et al. 2011; Frye et al. 2013; Bjørklund et al. 2020; Oh et al. 2020; Xie et al. 2021). Contrarily, fatty acid

palmitate was shown to be increased in ASD plasma samples. Palmitic and stearic acid and omega-6 fatty acids are also demonstrated to cause neuroinflammation and hence τ-phosphorylation and its aggregation in AD disease models. Palmitate is implicated as an intracellular signaling molecule that regulates the progression of several pathologies as diverse as cardiovascular diseases, neurodegenerative diseases, cancer, etc. (Fatima et al. 2019). It has also been proposed that metabolic modifiers precede the onset of neurological symptoms.

2.7 Enteric Microbiome Alterations Modulate Mitochondrial Function in ASD and AD

The enteric microbial flora (microbiome) influences the physiological and biochemical status of humans. In the last two decades, understanding the gut microbiome function in influencing health and disease has gained considerable scientific interest. The communities of microbial cells that harbor within the gut are involved in processes as diverse as metabolism, nutrition, and the host's immune regulation (Guinane and Cotter 2013). Besides a positive effect on human health, some microbial cells also release chemical mediators that can potentially disrupt normal cellular pathways, including mitochondrial functions. Diseases like gastrointestinal complications, diabetes, and autism have been attributed to a microbiome-mediated disruption in addition to other associated mechanisms. The chemical mediators secreted by the microbes residing in the gut can travel through the bloodstream, penetrating the blood-brain barrier (Guinane and Cotter 2013; Burokas et al. 2015). Studies have identified that behavioral symptoms in autism can aggravate with alterations in the diet and changes in the gut microbiota through early antibiotic exposure, perinatal infection, hospitalization, etc. The gut microbe produces short-chain fatty acids (SCFA) upon dietary carbohydrates fermentation, which serve as an essential trigger to modulate mitochondrial functions and other cellular regulatory pathways (Saint-Georges-Chaumet and Edeas 2016). These SCFA produced by gut microbes, most notably propionate, have been concomitant with the development of ASD to affect mitochondrial function (MacFabe 2015) directly. Some microbial products induce a damaging immune response in their immediate vicinity and travel to invade the blood-brain barrier inducing a pro-inflammatory state in the sentinel microglia. This pro-inflammation is associated with derangement in the normal mitochondrial functions and progression toward hypoxia as well as neuroinflammatory and epigenetic modifications (Siniscalco et al. 2013; MacFabe 2015). An SCFA component, propionate, is demonstrated to increase anti-nitrotyrosine immunoreactivity indicating oxidative stress. Propionate is also demonstrated to increase glutamate cysteine ligase modifier (GFA), a marker of immunoreactivity, and reactive astrocytes in the hippocampus of ASD subjects (Edmonson et al. 2014).

The microbiota of the intestinal system is altered as a result of unhealthy lifestyles such as food, sleep problems, circadian rhythm disturbance, and sedentary routines. Multifactorial changes spanning quantitative and qualitative differences have been

documented in the gut microbiome of AD patients and are considered a significant risk factor for sporadic pathogenesis of AD. Studies using specific pathogen-free mice and microbiome-reconstituted mice models have revealed increased brain-derived neurotrophic factor (BNDF) in the amygdala and reduced serotonin receptor (5HT1A) mRNA and NR2B subunit of the N-methyl-D-aspartate (NMDA) receptor mRNA expression. Also, in the hippocampus, this decrease is associated with an insufficiency of working and spatial memory (Neufeld et al. 2011). In another study, intestinal dysbiosis induced through ampicillin reduces the mineralocorticoid level and NMDA receptors in the amygdala, impaired spatial memory, and increased test animals' aggressiveness. However, this was restored through the *Lactobacillus fermentum NS9* strain as a part of the intestinal microbiome (Wang et al. 2015). Studies using matched cohorts have also pointed toward an association of microbiome composition with AD (Haran et al. 2019). Metagenomics complemented by clinical data has also confirmed a nexus between microbiome disturbance, neuroinflammation, intestinal disturbances, and AD/ASD disease.

The presence of acute stress and infection with conditional pathogenic bacteria *Citrobacter rodentium* are also reported to cause memory disorders in C57BL/6 mice (Gareau et al. 2011). A study conducted by Alzheimer's Disease Research Center (Wisconsin, USA) in 2017 demonstrated marked changes in the gut microbiome of AD patients matched to healthy individuals. This study decreased bacterial numbers belonging to *Firmicutes* and *Actinobacteria* phyla (particularly genus *Bifidobacterium*), and a surge in Bacteroidetes and *Proteobacteria* phyla bacteria in the gut microflora of AD patients was observed. Hence, the study distinctly demonstrated that intestinal microflora's functional component and taxonomy influence brain functions (Vogt et al. 2017). The human intestinal microflora has a direct regulatory role that works along the gut-brain-mitochondrial axis, modulating the development of neurological diseases such as ASD and AD.

2.8 Biomarkers of AD and ASD Linked to Mitochondrial Dysfunction

The pathological markers of AD include β-amyloid and τ-accumulation in the brain of AD patients. τ-protein regulates microtubule stability. However, modified τ aggregates in the neurons and is identified as a significant player in neurodegenerative diseases. In mice studies, τ-ablation has been concurrent with the enhanced ATP production and improvement in attentive capacity and recall memory (Jara et al. 2018). Mechanistically, τ-deletion reduced oxidative damage, thereby restoring the mitochondrial pro-fusion state besides inhibiting mitochondrial PTP formation, thus enhancing positive mitochondrial dynamics. There are reports that β-amyloid and τ-protein accumulation and apolipoprotein E (APOE) genes (a sporadic AD risk factor gene) could trigger mitochondrial dysfunction, which exacerbates the pathology.

Another pathological marker of AD, amyloid precursor protein, APP, together with amyloid-β, has a more direct link with mitochondria as compared to τ-protein

(Zhang et al. 2021; Mantzavinos and Alexiou 2017). These proteins localize to mitochondrial membranes and interact with other mitochondrial proteins besides disrupting ETC and importing nuclear-encoded mitochondrial proteins. They are shown to increase the production of ROS. However, it is also reported that the declining function of disrupted mitochondria leads to the accumulation of β-amyloid proteins besides several other comorbidities of AD. However, the existence of feedback loops makes a blurred understanding of the cause and effect. Recent researches have revealed that a highly toxic oligomeric form of β-amyloid protein (OAβ) disrupts normal mitochondrial function leading to a cascade mechanism responsible for severe deficit in the energy deficits preceding the development of AD (Sackmann and Hallbeck 2020).

Though ASD is identified mainly through behavioral pattern changes, several pathological markers have recently been correlated with the disease, including biomarkers of fatty acid metabolism, buccal cell enzymology, apoptotic markers, and ROS alteration. Most of these biomarkers are directly related to mitochondrial dysfunction, indicating an active role of mitochondrial disruption in the pathogenesis of ASD (Rose et al. 2018). Environmental exposure to toxicants and microbiome metabolites vis-a-vis oxidizing microenvironment is demonstrated to modulate mitochondrial function in ASD models.

2.9 Mitochondrial Targeting as a Therapeutic Approach for ASD and AD

The current therapy for AD relies on administering either glutamate-NMDA receptor antagonist like memantine or cholinesterase inhibitors, such as galantamine, rivastigmine, and donepezil. However, drug therapy is not approved by the Food and Drug Administration (FDA) for treating symptoms of autism. Autism is usually treated through behavioral management therapy, speech language, nutritional therapy, cognitive behavior therapy, joint attention therapy, physical therapy, etc. Regardless of the underlying mechanism that finally results in the development of ASD and AD, early diagnosis and intervention would lead to better treatment outcomes. As the knowledge of these neurodevelopmental diseases' pathogenesis is advancing, the prospects of better treatments can be augmented with targeted approaches (Fig. 2.2). Besides the present methodology of the drug-based treatment, many novel therapies are being explored and are continually evolving. Some of the new treatment approaches are discussed here.

2.9.1 H_2S Therapy

As observed in AD and ASD, enhanced ROS production affects mitochondrial function, contributing to the onset of neurodegeneration. Immediate consequences of high oxidative stress include lipid and protein oxidation and mtDNA mutation that induces neuronal cell death. Hydrogen sulfide (H_2S) has been demonstrated to

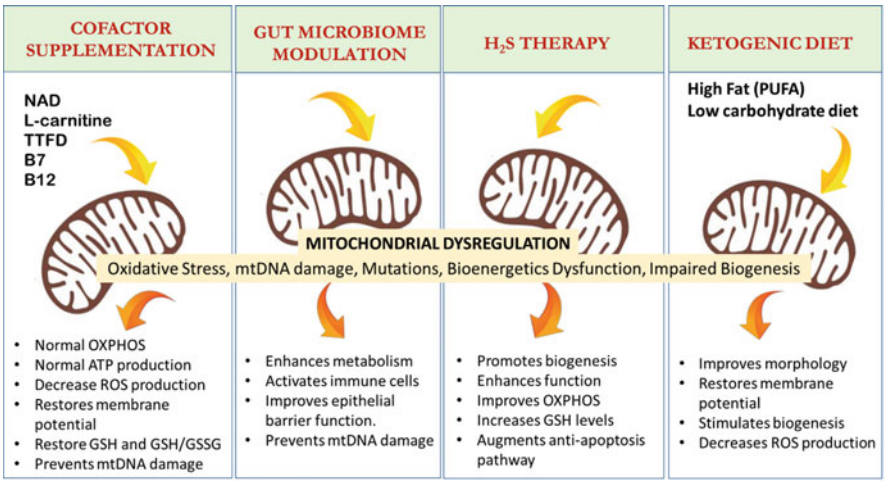

Fig. 2.2 Therapeutic modulation strategies for the restoration of mitochondrial dysfunction in ASD/AD patients

mitigate these effects of oxidative stress by elevating glutathione (GSH) concentrations through the potassium (K_{ATP}/K^+) and calcium (Ca^{2+}) ion channels. H_2S exerts its antioxidant effect through inorganic and organic compounds that mediate the activities of GSH, glutathione peroxidase, and superoxide dismutase, which in turn neutralizes hydrogen peroxide (H_2O_2)-induced oxidative damage.

Endogenously, H_2S is produced through pyridoxal phosphate-dependent enzymes in tissues, namely, cystathionine β-synthase (CBS), cystathionine γ-lyase (CγL), cysteine aminotransferase (CT), and 3-mercaptopyruvate sulfur transferase (MST). The normal level of H_2S for both plasma and tissue is 50–160 μM. CBS expression is very high in the hippocampus and cerebellum areas of the central nervous system (CNS). H_2S is a gasotransmitter that functions as a powerful antioxidant during the mitochondrial oxidation process to reduce oxidative stress generated in neurodegenerative diseases. Besides, H_2S can exert its protective effects as an anti-inflammatory molecule in the CNS to dissipate neuroinflammation (Zhang et al. 2017). Treatment with H_2S donor, sodium hydrosulfide (NaHS), has proven efficacy in suppressing hypoxia-induced neuronal apoptosis by blocking the H_2O_2-activated Ca^{2+} signal pathway. H_2S could also augment anti-apoptosis through nuclear translocation of nuclear factor kappa B (NF-κB) regulation (Zhang et al. 2017). Furthermore, the enzyme cystathionine γ-lyase (CSE), which produces H_2S, binds to τ-protein to exert its catalytic activity. Recently, this enzyme is shown to be depleted in AD human brains and 3xTg-AD mouse models, which leads to lower production and hence diminished concentrations of H_2S (Giovinazzo et al. 2021). Therefore, in the absence of H_2S, hyperphosphorylation of τ-proteins progresses as observed in AD. On the other hand, H_2S prevents this phosphorylation by sulfhydrating the τ-protein kinase, namely, glycogen synthase kinase 3β (GSK3β). This understanding has been furthered in the study by Giovinazzo et al. that

demonstrated the amelioration of both motor and cognitive deficits in AD upon administration of the H_2S donor sodium GYY4137 to 3xTg-AD mice (Giovinazzo et al. 2021).

2.9.2 Microbiome Modulation and Probiotic Therapy

ASD and AD have a compelling association with mitochondrial dysfunction. Besides, gastrointestinal symptoms are an essential indicator of ASD and are strongly associated with mitochondrial dysfunction. It is noticeable that the gut microbial flora can orchestrate immune modulation and inflammasome activation in both these diseases, as previously described. Furthermore, mitochondrial damage-associated molecular patterns (DAMPs) are signals to activate innate immunity. Hence, a cascade of molecular events triggered by a dysbiotic gut microbiome could stimulate the production of metabolites that target and damage mitochondria. Recent research has indicated that the plasma levels of pro-inflammatory cytokines such as IL-2, IL-4, IL-6, TNF-α, TNF-β, IFN-γ, etc. are significantly high in subjects with ASD. The increase in cytokines TNF-α and IL-6 is distinctly associated with the pathogenic gut microbiome, which constitutes the microbiota unique to ASD individuals in most of the disease cases. Beneficial gut microbiota, which includes *Lachnospiraceae and Bacteroides* and negatively correlates with pro-inflammatory cytokines, is present at reduced levels or absent in ASD (Cao et al. 2021). Hence, disturbances in plasma cytokine profile that link with alterations in the abundance of healthy gut microbiota in ASD patients could be considered an early diagnostic mechanism for ASD.

On the contrary, a specified microbial population with positive effectors harbors the ability to enhance oxidative capacity and be exploited as treatment strategies. Such a therapeutic approach holds the potential of slowing the onset of several metabolic and neurodegenerative diseases such as ASD and AD. Probiotics have shown promise in improving autistic symptoms by directly restoring intestinal microflora balance with subsequent positive effects in strengthening the gastrointestinal barrier. A study conducted on ASD children used four bacterial strains plus a prebiotic, fructooligosaccharide. It helped to normalize the gut microbiome and gastrointestinal functions, besides ameliorating the typical behaviors in autistic children. The probiotic therapy also increased the bacteria population, such as *Bifidobacteriaceae* and *B. longum*, which are beneficial. It reduced the existing potentially disease-causing bacteria such as *Clostridium* and *Ruminococcus* associated with autism symptomatology (Wang et al. 2020). Hence, probiotics are being tested as a promising treatment for ASD associated with gastrointestinal symptoms and can be utilized as a safe and effective treatment.

Future AD therapies can also involve the use of probiotics, especially as prophylaxis methodology, when mild cognitive impairment is observed or AD is first diagnosed. A healthy gastrointestinal tract harbors facultative anaerobic or microaerophilic *Lactobacillus* and *Bifidobacterium* species, which metabolize glutamate to produce gamma-aminobutyric acid (GABA). GABA is an important

inhibitory neurotransmitter in the CNS, and dysfunction of GABA is connected to dysfunction of synaptogenesis, cognitive impairment, and AD (Bhattacharjee and Lukiw 2013). Hence, restoring the typical microbiome in AD patients may have enormous effects and may facilitate customized microbiome manipulative strategies for the therapeutic management of AD and other neurodegenerative disorders.

2.9.3 Ketogenic Diet

A ketogenic diet has shown beneficial effects in children with ASD in improving the primary and associated symptoms of epilepsy. Unlike antiepileptic drugs, they are not related to adverse effects. The ketogenic diet exerts its beneficial effects, possibly through cerebral glucose metabolism, to improve mitochondrial morphology and white matter development in the brain. The ketogenic diet's positive influence has been observed in children with pyruvate dehydrogenase complex deficiency, with improvement in speech, language, and social functioning. In a case study, early initiation of a ketogenic diet has been associated with longevity and mental growth. From the mitochondrial standpoint, the ketogenic diet seems to be a promising therapy in both ASD and AD. In these neurodegenerative diseases, mitochondrial dysfunction and impaired bioenergetics can be salvaged through the use of ketone bodies. Ketone bodies can serve as the primary energy source for many metabolic processes instead of glucose. Besides, ketone bodies can exert neuroprotective effects by reducing glucose levels and increasing ketone bodies' formation by the liver. An increase in ketone bodies is mainly through the oxidation of polyunsaturated fatty acids (PUFA). PUFA increases peroxidases and reduces mitochondrial membrane potential and ROS through enhanced mitochondrial uncoupling protein expression (Milder and Patel 2012). A ketogenic diet also enhances the overall anti-injury potential of neurons by increasing global metabolic efficiency even under insufficient energy phases (Henderson et al. 2009). Ketogenic diet therapy seems to be a promising candidate as it can reduce inflammation and ROS generation, delay the progression of AD, and improve cognitive ability in AD patients.

2.9.4 Cofactor Supplementation

Besides many general cofactors that support improvement in the symptomatology of ASD and AD, nicotinamide adenine dinucleotide (NAD), thiamine tetrahydrofurfuryl disulfide (TTFD), biotin (B7), and methylcobalamin (B12) are imperative to healthy mitochondrial functions. Thiamine facilitates normal cellular energy metabolism, production of energy equivalence, and reduction of cellular ROS besides maintaining the structure and function integrity of mitochondria. At the same time, biotin attenuates the loss of mitochondrial membrane potential and reduces ROS production. Methylcobalamin (B12) is an integral cofactor for the regeneration of GSH and GSH/GSSG (James et al. 2004). It is vital for the proper functioning of the brain and nerves and red blood cell production. In a randomized

controlled trial, oral supplementation of cofactors (vitamin/minerals) for 3 months has shown improvement in the symptoms of autistic children besides improving methylation, glutathione, ATP, and NAD levels and reducing oxidative stress (Adams et al. 2011).

Additionally, L-carnitine is an amino acid derivative, which affects CNS and mitochondrial physiology. Studies have indicated altered metabolic channeling of L-carnitine in ASD patients (Demarquoy and Demarquoy 2019; Malaguarnera and Cauli 2019). Clinical trials are underway for the use of cofactor therapy in AD, focusing on metabolic improvement through dietary supplementation of L-carnitine tartrate, N-acetylcysteine, nicotinamide riboside, and serine. These studies aim to increase mitochondrial activity in the brain cell types through simultaneous dietary supplementation (ClinicalTrials.gov Identifier: NCT04044131) (Remington et al. 2016; Tardiolo et al. 2018; Peng et al. 2020). The cofactor therapies are well tolerated throughout a person's pathological status without any significant side effects or long-term detrimental effects. Many of the cofactors are water-soluble vitamin B supplements, which can be eliminated from the body through the kidneys.

2.10 Conclusion

Recent years have observed notable research advances in the field of mitochondrial disease. The development of advanced techniques that provide the ability to uncover novel mitochondrial gene mutations and associated metabolic derangements has immensely improved our understanding of molecular mechanisms that lead to mitochondrial dysfunction, which can influence a plethora of metabolic pathways including amino acid, carbohydrate, and lipid metabolism. Additionally, mitochondrial derangement also affects regulatory networks modulating apoptosis, calcium flux, hormonal and immunologic responses, and oxidative stress, eventually affecting the brain function. Mitochondria posit an inherent tendency to adapt to changing energy demands and microenvironments. However, increased environmental stress such as oxidative stress and diminished defense responses potentially induce structural and functional abnormalities in the mitochondria. Induced or genetic defects in the mitochondria thus act as the precursor of a plethora of neuronal disorders. In this review, we have provided an integrated perception of the major aspects of mitochondrial functional and structural abnormalities such as imbalance in calcium homeostasis, mitochondrial dysbiogenesis, gut microbiome alterations, mtDNA defects, etc. and their implications for neurodevelopmental and neurodegenerative disorders, namely, ASD and AD. Mitochondrial mechanistic failure is presently established as a significant event that impinges upon the progression of these diseases, and hence a potential target for therapeutic intervention.

Conflict of Interest The authors declare no conflict of interest.

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3 The Pathogenesis and Complications Associated with Autism Spectrum Disorder and Alzheimer's Disease: A Comparative Study

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disability that is associated with the promotion of social, communication, and behavioral inflexibility or impairment in an individual, whereas Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by degeneration and death of brain cells and ultimately leads to dementia and cognitive decline. However, reports suggest that both share common neuronal proteins including amyloid precursor protein (APP), phosphatase and tensin homolog (PTEN), fragile X mental retardation protein, and metabotropic glutamate receptors. Here, the correlation between neuronal proteins of these two diseases is highlighted. The significance of common signaling pathway is illustrated though the NOWADA model. The brain of individual suffering from ASD exhibits phenomenon of hyperplasticity that can be very crucial in tackling the AD. This study overview the medications approved for AD such as donepezil, galantamine, rivastigmine, tacrine and memantine, which have been also observed to be effective in ASD. More vigorous investigations are obligatory as there is an absence of medication for ADS and AD. Through overviewing the recent advances and trends regarding ASD and its correlation with AD can be fundamentally conducive in understanding mechanism of etiology of ASD and AD and formulating the ultra-efficient therapeutic approach to impediment complications due to these diseases.

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Keywords

Autism spectrum disorder · Alzheimer's disease · Neuronal proteins · Hyperplasticity · NOWADA model

3.1 Introduction

Autism spectrum disorder (ASD), simply referred as autism spectrum, is a group of neurodevelopmental disabilities that are associated with introducing the social, communication, and behavioral inflexibility and problems in an individual. It may also comprise autism, Asperger syndrome, Rett syndrome, and childhood disintegrative disorders. An individual always repeats such social, communication, and behavioral problems without having any interest modification from the complications. It has been reported in 2015 that around 1% of people are suffering from the autism spectrum which makes it near about 62.2 million people worldwide associated with this issue. The exact causes responsible for autism still remain unfold or unexplored to the world. In the initial 2 years of age of an individual, symptoms usually come into sight; that is why autism spectrum disorder is considered as a neurodevelopmental disorder.

Alzheimer's disease is a progressive neurodegenerative disorder characterized by degeneration and death of brain cells and ultimately leads to dementia and cognitive decline (Querfurth and LaFerla 2010). Trouble in memorizing the current events are the initial symptoms, difficulties in language and problems in behavior, and reduction in the muscle mass which weakens and ultimately leads to death (Querfurth and LaFerla 2010). The Alzheimer's disease cause is not explored yet clearly. Alzheimer's disease is known to be associated with protein misfolding diseases (proteopathy). Amyloid beta protein and tau protein are two proteins recognized to be responsible in causing Alzheimer's disease (Hashimoto et al. 2003).

Amyloid beta protein is structurally composed of 6–43 amino acids that are critically associated with Alzheimer's disease (Hamley 2012). It is regarded as intrinsically unstructured which is lacking the specific three-dimensional conformation. Amyloid beta is a portion of other bigger protein in the synapses of nerve cells known as amyloid precursor protein (APP). APP has the ability to penetrate into the membrane neurons and is very vital for the growth and development of neurons ("About Alzheimer's Disease: Symptoms," 2012).

Amyloid beta has been observed to cause the impairment, the death of neurons, and production of ROS (Hardy and Allsop 1991). It contains small portions of beta sheet and alpha helix structures, but it results into the formation of aggregates at higher concentration called amyloid fibrils, which is dominated by the presence of beta sheets. In the neuron cells, amyloid beta protein helps in the formation of lipid peroxidation and the formation of 4-hydroxynonenal. 4-hydroxynonenal is structurally an aldehyde group, which is toxic in nature, and found in cells formed during the process of lipid peroxidation (Hardy and Allsop 1991). The phenomenon of lipid peroxidation results in damaging the functioning of ATPases, transporters of

glutamate, and glucose. Thus, in the membrane where the transmission of nerve impulses occurs in the neurons, amyloid beta protein stimulates the phenomenon of depolarization, influx of calcium ion, and dysfunctioning of mitochondria (Mattson 2004). Reports suggest that the deficiency of amyloid beta protein is not exhibiting any noticeable absence of any role in the functioning. For the diagnosis of a patient suffering from Alzheimer's disease, no clear blood test is available in medical science; thus, signs and symptoms associated with Alzheimer's disease are usually exploited by doctors to diagnose this complication. Enzymes like gamma secretase and beta secretase are involved in the cleaving of APP into the minor parts (Hooper 2005). Among such minor fractions of APP, one of them results into the formation of amyloid beta, which ultimately bundles and accumulates exterior of neurons in compact structures referred to as senile plaques (Hooper 2005). The shape and size of senile plaque vary, but then its usual size is 50 μm which has a tendency to form protein aggregates and which functions as neurotoxic in nature.

Tau protein is a microtubule-associated protein (MAP), primarily found in neurons, and structurally is an isoform of six proteins formed via alternative splicing. In neurons, its role is to keep the microtubule in a stable condition. Tau proteins in hyper-phosphorylated form are coupled with the pathogenesis of Alzheimer's disease and Parkinson's disease (Goedert et al. 1991). Tau protein is phosphorylated through serine and threonine residues as these residues have binding sites for phosphorylation. The phosphorylation phenomenon is controlled by protein kinases especially serine threonine kinases. The proteoglycans including heparin sulfate are vital in the absorption of tau protein on the surface of cells by means of micropinocytosis process. It has been also observed that tau proteins play a crucial role in cell signaling and apoptosis (Ahanger et al. 2021a). There is obstruction of synapses by the misfolding and aggregation of tau protein. Some well-established reports depict that the Alzheimer's disease is caused due to protein misfolding or it is a proteopathy, in which the brain of the patient suffering from Alzheimer's disease is clumped due to aberrant amyloid beta protein (Ahanger et al. 2021b; Bashir et al. 2021). The brain cells or neurons have no tendency to be reversed after its death. Hence, there is lack of sustainable medicine for this fatal complication. But, in order to live with this suffering, scientists have suggested some therapeutic molecules, which provide the patient some sight of relief.

Acetylcholine is a neurotransmitter that is very crucial for the transmission of nerve impulse. Choline acetyltransferase is the crucial enzyme responsible for the synthesis of acetylcholine from choline and acetyl-CoA. Acetylcholine can be fragmented into choline and acetate in the presence of acetylcholinesterase. The action of acetylcholinesterase can be inhibited in order to design the therapeutic approach in various neurological complications including Alzheimer's disease. Taking clue from this approach, rivastigmine is a drug which has been found very effective as the blocker of acetylcholinesterase. Rivastigmine has been used in the preparation of nanoparticles, namely, cholesterol liposomal nanoparticles (Govindarajan Karthivashan et al. 2018). It has been found that in the brain, half-life of rivastigmine after conjugation with nanoparticle is enhanced significantly that contributes in its ability to tackle Alzheimer's disease. Reports have shown that there

are other important inhibitors of acetylcholinesterase such as catechin, which is very effective in the protection against various neurological diseases, when incorporated in gold nanoparticles (Govindarajan Karthivashan et al. 2018).

The genetic, neuroanatomical aberrations and environmental factors are thought to be the probable risk factors responsible for triggering the autism spectrum disorder. Reports obtained from MRI experiments suggest that people suffering from autism spectrum especially between the age group of 3 and 4 years possess a bigger total cerebral brain volume with respect to children which are at a verge of developing. Other reports depict that patients suffering from ASD from age group between 2 and 4 years also possess a larger brain volume with respect to the normal. Such uncharacteristic expansion of brain formation is due to extreme broadening of brain white matter and gray matter especially from the cerebral region. The H-MRS technique is very significant to identifying deformities and pathologies in brain sections that seem normal under MRI technique. From such experiments, N-acetyl aspartate choline, creatine, and myoinositol are some molecules with important spectral peaks. N-acetyl aspartate acts as an indicator which is very sensitive to structural stability of neurons. From the MRSI experiments, it is clear that people suffering from autism spectrum especially between the age group of 3 and 4 years shows that there is a reduction of *N*-acetyl aspartate. Such outcomes possess the significance for understanding the complexity of anomalous enlargement of the brain in the autism spectrum disorder. There is the assumption regarding the enlargement value of the brain in the patient suffering from ASD, which points it toward the impairment phenomenon of apoptosis or synaptic pruning. This suggestion depicts that as the concentration of *N*-acetyl aspartate elevates, it results into the formation of further compactly packed neurons or enlarged synaptic networks.

Immense measures of collective initiatives and associations such as Alzheimer's Disease Neuroimaging Initiative obtain and stake huge number of data including phenotypic, genotypic, behavioral, and imaging in order to assist in determining new biomarkers so to better apprehend the complexity of fatal complications. The extensively recommended approach which is the usual outline deals with the relation of the specific components symbolized in the form of nodes by the graph (Sarah Parisotb et al. 2018). In biomedical sciences, particularly, these nodes may signify the persons or patient observed in the possibly huge population, which comprises groups of characteristics, whereas the boundaries of the graph possess the relations of components and topics by the natural means. This type of demonstration permits to integrate the information about imaging and non-imaging data and personal characteristics all together, which may be used for the examination and pathology of brain diseases in huge populations (Sarah Parisotb et al. 2018). Many studies use the Graph Convolutional Networks, which involves ABIDE and ADNI, two huge datasets, in order to forecast the autism spectrum disorder and its transformation into the Alzheimer's disease, respectively. This demonstration from both databases depicts that this innovative arrangement may expand outcomes. The acquired results were with precision by means of ABIDE with 70% and ADNI with 80% (Sarah Parisotb et al. 2018). Downregulation of the immune system, inflammation (local reaction to cellular damage), oxidative stress (cellular damage caused due to the

inequality between free radicals and antioxidant), mitochondrial impairment, and exposure to environmental toxicants are some major physiological aberrations which are coupled with autism spectrum disorder (Fry and Frye 2012).

3.2 Materials and Methods

3.2.1 Comprehensive Study of Review of Literature of Different Neuronal Proteins

The basic material is acquired from the vigorous study of different previously authentic publications. Different neuronal proteins including amyloid precursor protein (APP), fragile X mental retardation protein, metabotropic glutamate receptors, and phosphatase and tensin homolog (PTEN) in association with autism spectrum disorder and Alzheimer's disease were thoroughly studied and reviewed. Various cell signaling pathways comprise NOTCH, WNT proteins of Alzheimer's diseases, and the protein of apoptosis pathway. All these pathways are collectively referred to as NOWADA model or NOTCH-WNT-Alzheimer's Disease-Apoptosis model. This vital pathway is comprehensively highlighted in this chapter (Fig. 3.1).

3.3 Discussion

There are many reports that suggest a link between autism spectrum disorder (ASD) and Alzheimer's disease (AD). Patients especially children suffering from autism have shown an increased percentage of amyloid precursor protein in plasma (Sokol et al. 2006). It has been observed that such patients exhibit two times the quantity of amyloid precursor protein as compared to patients suffering from mild autism spectrum disorder. Generally, it is estimated that a greater amount of soluble amyloid precursor protein-alpha results in insignificant reduction of Aβ40 in patients suffering from autism (Sokol et al. 2011). Such observations indicate that there are more chances of formation of higher proteins which are non-amyloidogenic in nature with anabolic behavior in autism spectrum disorder as compared to Alzheimer's disease which are dominated by catabolic behavior (Sokol et al. 2011). Increased amount of soluble amyloid precursor protein-alpha formed by means of non-amyloidogenic phenomenon might be involved in the complexity of autism spectrum disorder. There is a genetic disorder which is involved in intellectual disability called fragile X syndrome (FXS). The phenotypes responsible for mental retardation, introducing the social, communication, and behavioral problems in an individual, are called FXS phenotypes. Enhancement in the formation of soluble amyloid precursor protein-alpha through non-amyloidogenic phenomenon might be backing to phenotypes of both autism spectrum disorder and fragile X syndrome. The neurological disorder where there is an absence of a well-developed brain, especially in the newborns, which results into the development of a smaller than normal head is referred to as microcephaly. Increased levels of soluble amyloid

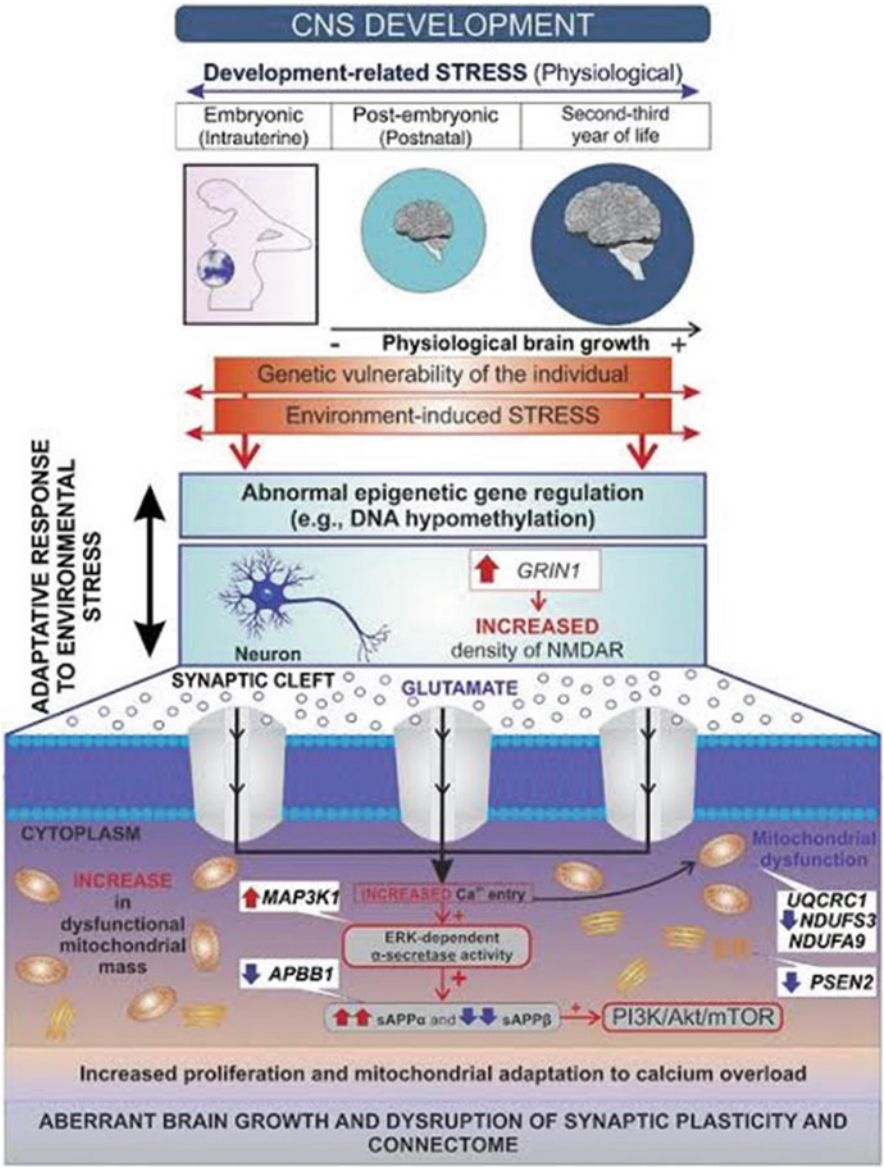

Fig. 3.1 Different abnormal neuronal proteins associated with autism spectrum disorder and their influence on neuroplasticity (Zeidan-Chulia et al. 2014)

precursor protein-alpha are also believed to be associated with microcephaly. Such kind of involvement of soluble amyloid precursor protein-alpha is partly facilitated by binding of sAPP-alpha to catenin. Cortical neurons are changed by adhesion and

migration due to sAPP-alpha to catenin thus stimulating this abnormal development of the brain.

The abrupt uncontrolled electrical signals between the neurons are referred to as seizures. It has been found that patients suffering from autism spectrum disorder, fragile X syndrome, and Alzheimer's disease are also characterized with possessing 10–30% of seizures (Hagerman 2002; Scarmeas et al. 2009).

3.3.1 Different Neuronal Proteins Associated with Autism Spectrum Disorder and Alzheimer's Disease

3.3.1.1 Amyloid Precursor Protein (APP)

Amyloid precursor protein (APP) is a bigger fraction of amyloid beta protein largely located in the synapses of nerve cells. It is present in many tissues but is largely located in synapses of nerve cells. The arrangement of different subcellular components in the presynaptic and postsynaptic locations for transmission of nerve impulse is controlled through the process called synapse formation. APP plays an important role in the process of synapse formation. The significant modifications exhibited by the neurons of the brain due to cortical reorganization are also facilitated by amyloid precursor protein, and the tendency is called neuroplasticity. Further, the enabling of exportation of iron is also an important biological function of amyloid precursor protein (Rogers et al. 2008). The export of iron is enabled by binding of APP with ferroportin and due to the presence of ferroxidase activity observed in APP, and this activity can be suppressed by the zinc ion (Rogers et al. 2008). In addition, the neuronal transport of molecules produced in neurons transported into synapses of neurons in the distal portion is also facilitated by amyloid precursor protein (Satpute-Krishnan et al. 2006). This transport is meditated by binding of cargo protein with kinesin protein. This type of transport is called anterograde neuronal transport (ANT), which occurs by transport of neuron molecules from the cell body outward into the synapse portion of neurons (Satpute-Krishnan et al. 2006). The gene present in humans which is responsible for encoding glutamate receptor is called metabotropic glutamate receptor 1 protein (mGluR1). The receptor, which functions by means of secondary messenger, is regarded as metabotropic receptor. It has been suggested that during the cell culture, there is the stimulation of glutamate receptor 1 which in turn leads to the enhancement in the release of soluble amyloid precursor protein (Jolly-Tornetta et al. 1998). In addition, there are reports which suggest that during cell culture, amyloid precursor protein is also associated with adhesion of nerve cells which signifies that this protein might also be vital in prevention. Hence, the position and role of APP in the autism is important for normal growth and development of the brain (Geschwind 2009).

3.3.1.2 Fragile X Mental Retardation Protein (FMRP)

Fragile X mental retardation protein (FMRP) is a vital protein, which is crucial for normal growth and development of the brain. There is development of FXS, ASD,

Parkinson's disease, mental retardation, and POF when the FMRP gene undergoes mutation (Verheij et al. 1993). Transportation of target mRNAs and guiding the phenomenon of translation at the synapse are major effects of FMRP. It has also been linked to interact with the assembly of ribosomes connected to the molecule of mRNA (Weiler et al. 1997). This interaction tendency of FMRP is operative in the presence of H homology domain, and glycine-arginine rich residues facilitated by controlling translation are apparently crucial for usual memory and learning (Weiler et al. 1997). The proximal portion of dendrite is the site involved in the formation of fragile X mental retardation protein, whereas distant portion of a dendrite is involved in transmission of nerve impulse synapse after the stimulation from mGluR (Miller et al. 2005). In patients suffering from fragile X syndrome, there is a rise in amount of dendritic spines in an immature form, which signifies that the morphology of the spine is irregular and uncharacteristic in nature (Sokol and Edwards-Brown 2004). Deficiency of fragile X mental retardation protein has been also linked with the formation of anomalous dendritic spine, which is a membranous outgrowth from the dendrite of a neuron crucial for the transmission of nerve impulse (Sokol and Edwards-Brown 2004).

3.3.1.3 Metabotropic Glutamate Receptors (mGluRs)

Metabotropic glutamate receptors (mGluRs) refer to glutamate receptor or type of GPCRs situated in the synapses of nerve cells, which function as metabotropic in nature, i.e., functions in the presence of secondary messenger (Bonsi et al. 2005). mGluRs interact with the excitatory neurotransmitters glutamate (Bonsi et al. 2005). mGluR is involved in the phenomenon of translation through triggering the different cell signaling pathways such as PI3K/mTOR pathway that is based on the fragile X mental retardation protein pathway (Lahiri et al. 2002). There are different subclasses of mGluRs and mGluRs 1, which have been observed to be responsible for causing the complications like Fragile X syndrome. The most frequently reported cause of autism spectrum disorder is Fragile X syndrome. mGluRs I are recognized to enhance the functioning of *N*-methyl-D-aspartate receptors which are important sites in causing excitotoxicity (excessive stimulation of glutamate receptor by the increase in glutamate that leads to damage and death of neurons) (Skeberdis et al. 2002). Metabotropic glutamate receptor II acts as agonists very important in the treatment of mood swings or mania or depression which are the peculiarities of a prolonged mental health complication known as schizophrenia (Krystal et al. 2003).

3.3.1.4 Phosphatase and Tensin Homolog (PTEN)

PTEN is an important human protein that functions as the tumor suppressor gene due to its phosphatase activity. The tensin domain and the catalytic domain are the two types of domains found in the structure of PTEN protein (Steck et al. 1997). Phosphatase activity in PTEN is responsible for tumor suppression. This phosphatase activity possessed by the protein PTEN is also very significant in cell cycle control, stopping cells from increasing and dividing too promptly (Steck et al. 1997). There can be more susceptibility in the formation of various cancers if this PTEN gene undergoes mutation. There is the formation of structure of lesions in the

cerebellar portion causing a disease called dysplastic gangliocytoma of the cerebellum characterized by the presence of mutated PTEN (Pilarski and Eng 2004). The study also suggests that there is the development of autism complications if the PTEN gene goes through any defects or abnormalities. The protein PTEN has been observed to be involved in the binding with the tumor suppressor protein called Tp53. This interaction results in the reduction in formation of energy in the nerve cells. This energy crisis in neurons results in destructive changes in the DNA of mitochondria with formation of energy in an abnormal way in different portions of the brain which is very vital for an individual's social behavior (Steck et al. 1997). The deficiency of PTEN protein leads to the binding of PTEN to p53 which initiates insufficiencies and abnormalities of different proteins observed in patients suffering from incapacities in learning such as autism spectrum disorder (Napoli et al. 2012). The structural change of various PTEN proteins is a key distinguishing trait seen in people suffering from autism spectrum disorder. This condition in which an individual is characterized with having an enlarged and abnormal head is called macrocephaly (Kerrr et al. 2006).

3.3.1.5 Correlation Between Amyloid Precursor Protein (APP), Fragile X Mental Retardation Protein, and Metabotropic Glutamate Receptors

There are reports which illustrate the significant governing correlation between amyloid precursor protein (APP), fragile X mental retardation protein, and metabotropic glutamate receptors with respect to autism spectrum disorder and Alzheimer's diseases (Westmark and Malter 2007). When the synaptic terminal is isolated from the nerve cell, it is called a synaptosome. When the synaptosome is resealed at postsynaptic level, it is called a synaptoneurosome. There is enhancement of amyloid precursor protein (APP) in protein synthesis when the synaptoneurosome is activated in the presence of metabotropic glutamate receptors (Westmark and Malter 2007).

The complex formation between RNA and protein in the presence of amyloid precursor protein (APP) and fragile X mental retardation protein mRNA has been observed to be denatured via agonist behavior exhibited by metabotropic glutamate receptors in animals especially wild type (Westmark and Malter 2007). With basal conditions, fragile X mental retardation protein is involved in the suppression of translation of amyloid precursor protein. However, this suppression is operative once metabotropic glutamate receptor 5 is stimulated and activated. The suppression of amyloid precursor protein is lacking which is based on translation of fragile X mental retardation in fragile X syndrome (FXS) (Vanderklish and Edelman 2002). Studies also suggest that increase in the translation of amyloid precursor protein is not observed to be activating the amyloidogenic pathway of amyloid precursor protein. This ultimately can facilitate the additional substrate for the enzyme such as alpha-secretase pathway and possibly display significant neuroprotection from the lethality of Alzheimer's disease. Specifically, this would describe the deficiency of Aβ plaques detected in fragile X syndrome and in autism spectrum disorder (Vanderklish and Edelman 2002).

3.3.1.6 Significance of NOWADA Model in Alzheimer's Disease and Autism Spectrum Disorder

There is web of various cell signaling proteins associated with Autism Spectrum Disorder such as Notch, Wnt, proteins of Alzheimer's disease, and the proteins of apoptosis pathway. Notch protein refers to transmembrane protein responsible for cell-cell communication and regulating the fate of the cell at the time of development. Wnt protein is a glycoprotein involved in Wnt signaling pathways responsible for the interaction between cells either cell-cell communication or same-cell communication and controlling of developmental processes, and this protein has been also observed in association with ASD (Zeidan-Chulia et al. 2014). There are at least 374 proteins in this model, which are interrelating with each other by means of 3665 interactions. These proteins result into the formation of some nodes with various categories: Notch, Wnt, AD, or apoptosis. These networks of proteins have been observed in patients suffering from autism spectrum disorder in the cerebellar portion of the brain (Zeidan-Chulia et al. 2014). The network of such complex of proteins is believed to be a mutual pathway existing between the etiology of Alzheimer's disease and autism. In silico studies depict that there are two therapeutic molecules such as magnesium and rapamycin that exhibit significant effects on proteins associated with NOWADA model.

Rapamycin Rapamycin is a conjugated molecule that acts as antibiotic and has been observed to be involved in the suppression of B cell and T cell process of activation by decreasing the sensitivity of IL-2 via suppression of mTOR. But nowadays, it is believed that rapamycin can be significant in the prevention of autism spectrum disorder (Spilman et al. 2010). Studies from mice tell us that rapamycin could be involved in restoring the synaptic plasticity and enhancement of transmission of nerve (Ehninger et al. 2008; Spilman et al. 2010).

Magnesium Magnesium serves as the cofactor and possesses the catalytic effectiveness in the hydrolysis of GTP. The enzyme serine threonine kinase containing proline is known as glycogen synthase kinase-3 beta or simply the GSK3B (Zhang et al. 2000). Its phosphorylating activity is based on the substrate of magnesium. Its mutation has been coupled with neurological complications including bipolar disease and Alzheimer's disease (Zhang et al. 2000). There are studies which illustrate that the decreased level of magnesium has been observed markedly in the brain of individuals suffering from autism spectrum disorder; correspondingly, a decreased level of magnesium has also been observed markedly in the brain of individuals suffering from Alzheimer's disease with respect to normal brains (Strambi et al. 2006). In recent times, there are studies which show that the increased level of magnesium in the brain performs a vital role and results in the neuroprotective effects in the synapses portion in individuals suffering from Alzheimer's disease. Therefore, magnesium could be used as a therapeutic strategy in order to tackle Alzheimer's disease. There are also reports of progressive communicative effects of magnesium in the presence of pyridoxine treatment with respect to the treatment of autism spectrum disorder (Strambi et al. 2006).

3.3.1.7 Neurotoxic Nature of Aluminum as the Inducer of Autism Spectrum Disorder and Alzheimer's Disease

Aluminum is the commonly observed and most extensively used metal on the surface of the planet. Approximately 52 million tons of aluminum are produced annually throughout the world. The report suggests noncarcinogenic nature of aluminum in humans. Aluminum is harmless or nontoxic in nature up to 40 mg per day. Aluminum oxide has been used as food additive, coloring agent, emulsifying agent, and thickener. It is also reported in humans that aluminum oxide has been associated in the formation of numerous neurological complications such as Alzheimer's disease and autism spectrum disorder (Virk and Eslick 2015). Ample reports are there which illustrate that aluminum shows a neurotoxic behavior in humans and might be a very critical inducer in the pathogenesis of Alzheimer's disease, autism spectrum disorder, and some gradual, neurological complications based on age (Virk and Eslick 2015). Hence, it is believed that such types of contact circumstances to aluminum can harmfully deteriorate human health. In other studies, involving a postmortem examined human brain, there was an increased level of aluminum which could be suggestive to be associated with Alzheimer's disease (Aileen Pogue 2016). It is also observed that toxicity of aluminum can be a causative agent for degeneration of the central nervous system, which can especially lead to the formation of encephalopathy (malfunction and damage of the brain) (Aileen Pogue 2016).

3.3.1.8 Correlation in Therapeutic Approach Approved for Autism Spectrum Disorder and Alzheimer's Disease

As far as treatment of autism spectrum disorder is concerned, there are only two drugs for the treatment of autism spectrum disorder, risperidone and aripiprazole. These therapeutic molecules are approved by the Food and Drug Administration (FDA) not for the primary symptoms of this complication but for countering the irritability complication associated with ASD. There are some treatments which have been observed to be effective in treating the symptoms associated with autism spectrum disorder, and among them there are also some medications which are also effective and recommended in the treatment of Alzheimer's. According to US FDA, donepezil, galantamine, rivastigmine, tacrine, and memantine are few molecules which have been accepted as effective therapeutic strategy for Alzheimer's disease. Such molecules are responsible for obstructing and blocking the usual breakdown of the neurotransmitter acetylcholine, referred to as cholinesterase inhibitors.

3.3.1.8.1 Donepezil

Donepezil is structurally a hydrochloride salt derived from piperidine, which is approved for the treatment of Alzheimer's disease. Donepezil is observed to be interacting with cholinesterases and deactivates the activity of this enzyme, thereby by obstructing acetylcholine from the breakdown (Anas Shamsi et al. 2020). At synapses, this ultimately leads to increases in the level of acetylcholine (Kumar and Sharma 2020). However, its exact mechanism of action is still not explored yet.

There are reports which depict that 70% of patients suffering from autism spectrum disorder have shown improvement (Anas Shamsi et al. 2020). Studies have shown that in patients suffering from autism spectrum disorder, children from the age group of 2.5–6.9 years have disturbances in rapid eye movement (REM) sleep (Buckley et al. 2011). Upon administration of the drug donepezil to these patients, there has been an enhancement in the level of REM sleep (Buckley et al. 2011). In other studies, before donepezil was administered, particularly in children aged 5 years, patients showed symptoms of lacking communication, eye contact, and hyperactivity (Srivastava et al. 2011). Upon administration, a marked enhancement in communication, eye contact, and hyperactivity was seen. Still, there are inconsistent evidences regarding the improvement from symptoms of ASD with the use of donepezil (Srivastava et al. 2011).

3.3.1.8.2 Galantamine

Galantamine is a benzazepine derivative of norbelladine which acts as a cholinesterase blocker. It is approved for different memory loss problems and treatment of Alzheimer's disease. Galantamine obstructs the acetylcholinesterase, which is responsible for the breakdown of the neurotransmitter acetylcholine. This suppression of acetylcholinesterase results in the rise of neurotransmitter acetylcholine significantly for transmission of nerve impulse. Studies suggest that galantamine can be administered in patients suffering from autism spectrum disorder especially to children (Ghaleiha et al. 2013). Upon administration of this drug, there has been an observance of removal of the social irritability and lethargy (Ghaleiha et al. 2013). In other studies, suggesting administration of 16 mg per day of galantamine in patients suffering from autism spectrum disorder especially adults from the age group 21–25 years, there is enhancement in the expression of language and communication. It is assumed that galantamine is possessing dual activity as it has been exhibiting parallel effects in both children and adolescent patients suffering from autism spectrum disorder (Nicolson et al. 2006).

3.3.1.8.3 Rivastigmine

Rivastigmine is a carbamate ester which acts as a cholinesterase blocker and is approved to treat neurological complications including Alzheimer's disease and Parkinson's (Khoury et al. 2018). It has been observed that rivastigmine is involved in the suppression of butyrylcholinesterase activity as well as acetylcholinesterase. It is also reported that the pathway associated with the activity of alpha-secretase can be modified in the presence of rivastigmine (Khoury et al. 2018). Another study suggests that rivastigmin (0.8 mg twice a day) when administered to patients (children) suffering from autism spectrum disorder leads to enhancement of communication (Chez et al. 2004b). Such improvement in the communication has been observed statistically substantial for therapeutic approach and provides optimistic healing effects in the individuals suffering from the autism spectrum disorder (ASD) (Chez et al. 2004b).

3.3.1.8.4 Tacrine

Tacrine chemically belongs to the class of acridines, regarded as blocker of acetylcholinesterase, and has been recommended for the treatment of Alzheimer's disease (Taraschenko et al. 2005). The tread name of tacrine is Cognex in the market (Taraschenko et al. 2005). Tacrine is easily soluble in distilled water, 0.1 normal solution of HCl, dimethylsulfoxide, methanol, ethanol, and propylene glycol, and in both the buffers including phosphate buffer and acetate buffers (Taraschenko et al. 2005). Reports suggest that 20 mg of tacrine can be given to autism spectrum disorder patients especially in the age group 17–33 years. Upon administration of this drug, there has been an observance of recovery from bad temper and unfitting communication-like symptoms (Niederhofer 2007).

3.3.1.8.5 Memantine

Memantine is a primary aliphatic amine, which acts as a blocker of acetylcholinesterase, and is approved as medication for Alzheimer's disease. Excessive release of glutamate results in the repeated stimulation of glutamate receptors. This repeated stimulation results in the deterioration and death of neurons. This process is called neuronal excitotoxicity. This excitotoxicity phenomenon has been assumed to be responsible for the pathogenesis of Alzheimer's disease. The *N*-methyl-D-aspartate receptor (NMDA receptor) provides an innovative method to understand the narrow effectiveness of present medications aiming the cholinergic system.

Memantine is reported to be interacting with NMDA receptor. The binding affinity of this interaction is excellent; thereby, memantine is able to conquer the continued entry of calcium ions, predominantly from the extrasynaptic receptors involved in neuronal excitotoxicity. Thus, memantine is involved in the suppression of neuronal excitotoxicity and reserves the role of the receptor at synapses. Hence, the binding of memantine to glutamate receptors or NMDA receptors is very significant in the symptomatic enhancement.

There are several studies which describe the effectiveness of memantine administrated in patients suffering from autism spectrum disorder. Reports suggest that 8.1 mg per day of memantine drug (Chez et al. 2004a) provides recovery from bad temper and unfitting communication-like symptoms, further improving attention and language (Chez et al. 2004a). In another study, 20 mg per day dose of memantine was administered (patients aged 6–19 years) showing progress in social withdrawal and carelessness (Erickson et al. 2007). However, a few patients experienced increase in side effects such as irritability, rash, and seizures with this medication (Erickson et al. 2007).

Numerous reports have delineated contradictory effects in some individuals suffering from ASD after the medication of memantine (Rossignol and Frye 2014). Remarkably, memantine has been described to both recover and deteriorate the irritability. Such studies indicate that there can be particular subcategories of children suffering from ASD which react significantly to memantine (Rossignol and Frye 2014). Evidently bigger, well-made, and vigorous investigations are required to further assess the effectiveness of memantine in patients suffering from ASD

especially children and also subcategories that may significantly react to medication of memantine (Rossignol and Frye 2014).

3.3.2 Role of Neuroplasticity in Autism Spectrum Disorder and Protection from Alzheimer's Disease

Due to proliferation of cells, there is organ enlargement, which is called hyperplasia or hypergenesis or neoplasia or benign tumor. The condition of being hyperplastic is known as hyperplasticity. Many times, hyperplasticity condition may be harmless, which takes place in some specific tissues (Sembulingam and Sembulingam 2012). During pregnancy, glandular cells in the breast that are responsible for secreting milk undergo growth and multiplication. This is an excellent instance of hyperplastic response (Dirbas and Carol 2011). The innate ability of brain neurons to form and reorganize or modify their synaptic connections and behavior in response to new information, injury, or dysfunction is known as neuroplasticity (Davidson and Bruce 2012; Doidge 2007). These changes occur from the cellular level (neurons) to extensive level comprising cortical remapping. In the cortex of the brain, there is an assembly of minicolumns (vertical column) responsible in executing particular information including texture, color, and outline maps; it is called cortical maps (Doidge 2007). The phenomenon through which the brain is influenced and stimulus results in the formation of the cortical map which is new is known as cortical remapping (Doidge 2007). Thus, neuroplasticity is some sort of hyperplasticity in which the brain adjusts some significant changes such as training and acquiring new abilities that may be learning languages, math, and also physical activities and strength (Compare: Reznikov et al. 2012). The phenomenon in physical activities is involved in the initiation of motor cortex which ultimately is responsible for enhancing the connectivity between your brain and your body, which is regarded as neuropriming. During the event of neuropriming, the brain goes into a state of profound plasticity so that brain acclimatizes such physical activities more efficiently through the process of hyperplasticity (Livni 2019). The physical activity which involves the building of robust networks of the brain with the muscles by means of neurostimulation is called neuropriming (Livni 2019). It involves the phenomenon of hyperplasticity or hyper-learning. There is the headset that permits the operator to increase any physical ability rapidly through the use of neuropriming mechanism, and this headset is called halo sport (Livni 2019).

Thus, the soundness of the brain is reliant on sustaining a suitable equilibrium at the cellular level and extensive level of cortical plasticity (Freitas et al. 2013). In cortical plasticity, gradual deterioration at the cellular level (neurons) of the brain involves modifications which are associated with the age of an individual and a compensating rise in extensive level of cortical plasticity (Freitas et al. 2013). It has been observed that individuals suffering from ASD are also suffering from age-linked cognitive and behavioral problems. There is, however, no indication that people with ASD have a shorter lifespan than the rest of the population. This report shows that patient suffering from ASD can also sustain a significant tendency for

modulation throughout the lifespan. In the pathogenesis of dementia in Alzheimer's disease, there is the involvement of phenomenon of cascade prematurely which is believed to be driven by changes in synaptic plasticity. In these complications of the brain, there is accumulation of amyloid aggregates; tau protein-induced neuronal degeneration is also supposed to occur due to changes in synaptic plasticity (Oberman and Pascual-Leone 2013). The autism spectrum disorder is mostly associated with hyperplasticity. The hyperplasticity has been also reported to form a cascade by the involvement of various neuronal proteins which can provide the defense from the early offense of various neurological complications (Andrasi et al. 2005). Numerous reports indicate that neuroplasticity decreases during the course of the life cycle. It is further suggested that the cortex of the brain in patients suffering from autism spectrum disorder is exhibiting the hyperplastic response. Therefore, such complications must be prevented by decrease in the hyperplastic response (Oberman and Pascual-Leone 2013). It is reported that individuals suffering from autism spectrum disorder manifest hyperplasticity or brain plasticity through adulthood. This may be crucial for the prevention of the onset of Alzheimer's disease (Andrasi et al. 2005; Oberman and Pascual-Leone 2013). Figure 3.1 shows different abnormal neuronal proteins associated with autism spectrum disorder and their influence on neuroplasticity (Zeidan-Chulia et al. 2014).

In conclusion, the neurodevelopmental disability caused by autism spectrum disorder (ASD) and neurodegenerative complication caused by Alzheimer's disease (AD) are two dangerous diseases with debilitating consequence in the human health. However, research refers that both complications involve the same neuronal proteins such as amyloid precursor protein (APP), phosphatase and tensin homolog (PTEN), fragile X mental retardation protein, and metabotropic glutamate receptors. Therefore, there may be a strong relationship among these neuronal proteins with respect to the pathogenesis of these complications, so this study also describes such correlation. The significance of common signaling pathway is illustrated though the NOWADA model. Also, hyperplasticity is also a significant phenomenon in the brain of individuals suffering from ASD whose exhibition could be the possible key factor in the pathogenesis of AD. There is no medication available for the treatment of ASD; still, there are some drugs such as donepezil, galantamine, rivastigmine, tacrine, and memantine approved for AD. In ASD, acetylcholine and glutamate neurotransmitters in the state of impairment are targeted by such medications. Studies reveal that these drugs have also shown some improvement in a few symptoms of ASD. Therefore, further strong studies are recommended, as efficient medication for ADS and AD is unavailable. Through emphasizing the current advances and progress on ASD and its association with AD, this study focuses the importance on understanding the pathogenesis and complications associated with these disorders and urge to design effective medications for such a frustrating human disease.

Conflict of Interest The authors declare no conflict of interest.

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Impact of Common Natural Compound in the Treatment of Alzheimer's Disease

4

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Abstract

Alzheimer's disease (AD) is considered one of the most complex neurodegenerative disorders. Amyloid and tau pathology, along with neurofibrillary tangles, are most commonly seen in this disease. Various compounds show promising responses in treating this disease, but they also cause severe side effects. To minimize these side effects, researchers explored several natural products for the treatment of this disease. Natural products cause very minimal side effects as compared to isolated chemical compounds. The minimal side effect might be due to the complex synergistic effects of various bioactive components present in these natural products. Several natural products like green tea, epigallocatechin gallate, baicalein, berberine, and quercetin show a robust response in the treatment of AD. Some natural compounds like *Ginkgo biloba* extract and Huperzine

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A passed the clinical trial on PD. This chapter has explored the potential of some of the most common natural products to treat AD in a sequence-wide manner.

Keywords

Alzheimer's disease · Green tea · Epigallocatechin · Baicalein · Clinical trials

4.1 Introduction

Alzheimer's disease (AD) is a multifactorial and progressive disease of the brain that occurs worldwide. AD is also considered one of the most common forms of progressive dementia characterized by beta-amyloid and tau pathology (DeTure and Dickson 2019). Oxidative stress, neuroinflammation, mitochondrial dysfunction, and synaptic dysfunction are common factors observed in AD progression (Tönnies and Trushina 2017). Targeting mitochondrial dysfunction shows a better therapeutic response to stop the progression of this disease (Rai et al. 2020). Despite several treatment options, there is no holistic approach to stop the disease progression. Although several compounds have a strong potential to treat AD, several side effects limit their usage.

Consequently, researchers have shifted their attention toward natural compounds that might have significantly fewer side effects. Researchers have demonstrated that several natural products show enhanced therapeutic efficacy in treating AD (Dey et al. 2017; Shao and Xiao 2013). In this book chapter, we have discussed the role of some common natural products which are used to treat AD.

4.2 Green Tea in the Treatment of AD

In a recent study, green tea's neuroprotective role was evaluated in a rat model of AD. In this study, the authors demonstrated that cognitive functions were improved after green tea administration (Schimidt et al. 2017). In a similar work, the impact of green tea consumption on oxidative stress parameters was shown in 30 patients with chronic AD. Based on the antioxidant level improvement, they implicated that green tea could be added as a prophylactic agent in the AD therapeutic category (Arab et al. 2016). Zhu et al. aimed to conduct a study to improve synaptic efficiency to revive memory impairment in AD. The authors explored L-theanine's role, a natural constituent present in green tea, to achieve the memory improvement goal by altering hippocampal synaptic transmissions in transgenic experimental mice. They further suggested that L-theanine could modulate the hippocampal synaptic efficiency, consequently alleviating AD symptoms, hence could be considered as a therapeutic candidate in the AD treatment regime (Zhu et al. 2018). In a most recent study, green tea as cognitive impairment rejuvenating moiety in the form of the

dietary supplement was investigated. In the study, firstly, an extract was obtained from dried *Camellia sinensis* (CS) leaves and later was decaffeinated. Further in vitro and in vivo studies revealed a decline in beta-amyloid (Aβ42 and Aβ40) levels (Kim et al. 2019). Ali et al. carried a molecular docking study to examine green tea's effect on the level of acetylcholinesterase (AChE)- and butyrylcholinesterase (BChE)-dependent neurodegeneration in AD. They suggested green tea as a potential inhibitor of AChE and BChE with enhanced cholinergic neurotransmission for a prolonged period (Ali et al. 2016). Another investigation by Kaur et al. depicted that green tea extract exhibited therapeutic abilities for age-related cognition impairment in young and old male Wistar rats. The current study suggested that green tea could be employed as a potential therapy to reverse age-related deficits in learning and memory through selective acetylcholinesterase inhibition (Kaur et al. 2008). Another group evaluated green tea's constituent polyphenol epigallocatechin gallate (EGCG) to halt the aggregation cascade of Aβ and tau proteins. In vitro assays revealed that EGCG has the potential to prevent amyloid-like formation of β-sheet rich along with aggregates of tau. Hence, EGCG was found to be a potential candidate to attenuate Aβ by inhibiting the hallmarks of AD (Wobst et al. 2015). In another investigation, the antioxidant and antiapoptotic pathway inhibitor potential of green tea was studied in the primary cortical neuron. The authors quantified the level of reactive oxygen species (ROS) and superoxide dismutase (SOD) in the serum and performed Western blot. The study concluded tea polyphenol as potential therapeutics against glutamate-induced excitotoxicity and their protective effect mediated by the attenuation of oxidative stress and anti-mitochondrial apoptotic pathway (Lin et al. 2016). In a similar work, the antioxidant potential of EGCG was concluded based on the findings of behavioral and biochemical tests (Biasibetti et al. 2013). In another study, fish oil in combination with EGCG was administered in transgenic mice. The authors reported a decline in the therapeutic dose of EGCG due to possible synergistic effects. Eventually, enhanced inhibition of cerebral Aβ deposits was observed in the mice (Giunta et al. 2010).

Additionally, Lim et al. evaluated catechin of green tea to treat AD via free radical scavenging activity. The studies established a significant improvement in behavioral deficits utilizing shortening of escape latencies, escape distances, and swimming velocities in diseased mice. Hence, the authors demonstrated that catechin could be a potential therapeutic intervention in AD-related dementia (Lim et al. 2013). Another study employed multi-dimensional targeting approach of green tea component L-theanine to attenuate β-amyloid-induced cognitive dysfunction and neurotoxicity. Findings of the experiments concluded L-theanine as a potential therapeutic agent by declining extracellular signal-regulated kinase and p38 mitogen-activated protein kinase (ERK/p38) and nuclear factor κB (NF-κB) and by the reduction of macromolecular oxidative damage (Kim et al. 2009).

4.3 Therapeutic Role of Vitamins in AD

Fillenbaum et al. demonstrated that taking vitamin C and/or vitamin E alone did not delay dementia and AD in community-dwelling elders (Fillenbaum et al. 2005). Therefore, the authors finally suggested that supplemental vitamin C and/or E use alone is inadequate to delay dementia or AD. On the contrary, Boothby et al. investigated the potential of supplemental vitamin C and E in the treatment. They showed that the combined use of vitamin C and/or vitamin E reduces AD prevalence (Boothby and Doering 2005). One study explored the role of vitamin E along with donepezil for mild cognitive impairment treatment. The double-blind study results demonstrated no significant improvement in cognitive impairment with the combined use of vitamin E and donepezil. However, donepezil therapy displayed a lower rate of AD progression up to some extent (Petersen et al. 2005). Additionally, Refsum et al. confirmed the link between low levels of vitamin B-12 in AD. Finally, the authors' findings suggested that the level of cobalamine is impaired in AD and can be improved with the administration of B-12 (Refsum and Smith 2003). In another study, Kontush et al. explored the effect of vitamin E and C supplementation on lipoprotein oxidation in AD patients. They suggested that vitamin E and C significantly prevented autoxidation of CSF and plasma lipoproteins. So, the above findings documented that combined use of vitamin E and C supplementation provides a biochemical basis for AD (Kontush et al. 2001). Additionally, Li et al. evaluated the impact of dietary intakes of vitamin E, vitamin C, and β-carotene on AD's development. The meta-analysis results indicated a reduction in AD risk after taking vitamin E and C, along with β-carotene as dietary components (Li et al. 2012). Moreover, another study investigated the role of vitamin E in Alzheimer's disease (Lloret et al. 2009). In addition to this, in old-age conditions, Polidori et al. showed an enhanced level of carotid intima–media thickness and reduced levels of plasma vitamin C along with vitamin E. Biochemical results revealed that optimum level of vitamin C might be involved in protection against AD and other cognitive manifestations (Polidori et al. 2015). Takasaki et al. investigated the anti-oligomerization potential of vitamin A through in vitro studies on Aβ. They examined the oligomerization inhibitory effect of vitamin A on $A\beta_{40}$ and $A\beta_{42}$. Thus, based on the above evidence, author confirmed that vitamin A could be useful in AD prevention (Takasaki et al. 2014). In another similar study conducted by Huy et al., the anti-amyloidogenic potential of vitamin K3 analogs was shown via in silico and in vitro characterization for AD treatment. Both numerical and experimental results exhibited significant inhibition of Aβ aggregation and conformational conversion by different analogs. Moreover, cell viability results showed strong free radical reduction and protection against A-β-induced toxicity. Based on all these findings, the authors documented that modified vitamin K3 analogs could become a strong anti-amyloidogenic therapeutic candidate for AD (Huy et al. 2013). Moreover, Gezen-Ak et al. studied the effect of Apa1 and Taq1, two single nucleotide polymorphisms (SNPs) of vitamin D receptor (VDR) gene in 104 Alzheimer's participants. They concluded that the risk of AD was more in Apa1 heterozygotes (Gezen-Ak et al. 2007). In a similar finding,

Lehmann et al. confirmed the interaction of two VDR polymorphisms, i.e., Apa1 and Taq1, in the regulation of neuroinflammation in patients <75 years old (Lehmann et al. 2011). Meanwhile, another study examined the role of vitamin D in decreasing L-type voltage-sensitive calcium channels A1C (LVSCCA1C) levels and in causing the downregulation of cytotoxicity in the vitamin D treated group, resulting in upregulation of nerve growth factor (NGF) secretion compared to the control group. This study also determined that inhibition of Aβ toxicity prevents the alteration of cortical neuronal activity (Dursun et al. 2010). Moreover, Annweiler et al. showed that higher intake of dietary vitamin D leads to fewer chances of AD among women aged 75 years and older (Annweiler et al. 2012a).The same group studied a combination of memantine and vitamin D and demonstrated improvement in Mini-Mental State Examination (MMSE) score and cognition performance in patients with AD compared to drug alone (Annweiler et al. 2012b). Similar results were reported by another group (Pogge 2015). A meta-analysis performed by Zhao et al. revealed that a lower level of 25-hydroxy-vitamin D was observed in patients with AD and Parkinson's disease as compared to healthy control (Zhao et al. 2013). Additionally, Grimm et al. demonstrated that 25(OH)-vitamin D increases β-secretase BACE1 protein levels, responsible for an increase in Aβ peptide level. Vitamin D leads to upregulation of neprilysin (NEP) expression and consequent increase in Aβ degradation. They concluded the potential of vitamin D in the management of AD (Grimm et al. 2014). The same group reported the strong link between vitamin D deficiency in AD and other neurodegenerative disorders like PD and vascular dementia (Grimm et al. 2019). Additionally, other reports also found that development of dementia and AD is increased in vitamin D-deficient patients (Littlejohns et al. 2014; Afzal et al. 2014). Furthermore, Gangwar et al. demonstrated that the MMSE score was significant in the treatment group as compared to the control group. Thus, they indicated that vitamin D effectively improves cognitive functions and senile dementia in the elderly (Gangwar et al. 2015). In this regard, Oudshoorn and colleagues exhibited similar findings where MMSE score was higher in vitamin D-sufficient patients and suggested vitamin D_3 has an additional effect in enhancing cognitive performance in patients with AD (Oudshoorn et al. 2008). Mohamed et al. reported that vitamin D_3 exerts a neuroprotective effect in AD (Mohamed et al. 2014). Further, Mizwicki et al. reported that insufficiency of 1α,25 $(OH)_2$-vitamin D_3 (1,25D3) and resolvin D1 might involve a risk factor for the development of AD (Mizwicki et al. 2013). Recently, Fan et al. provided evidence that four potential targets encoded by genes CACNA1C, NOTCH4, COMT, and DRD3 show the important effect of vitamin D against AD and psychosis (Fan et al. 2020).

4.4 Epigallocatechin Gallate in AD

Zadeh et al. reported the potential of (-)-epigallocatechin-3-gallate (EGCG) to decrease the Aβ generation through in vitro studies using murine neuron-like cells (N2a). These cells were transfected with the human "Swedish" mutant amyloid

precursor protein (APP). They observed that EGCG significantly enhanced the cleavage of the α-C-terminal section of APP and lifted the N-terminal AP cleavage product, soluble APP-α. In this study, a reduced level of Aβ and plaque were observed. Finally, they concluded that EGCG could be used as a prophylactic treatment for AD (Zadeh et al. 2005).

In another study, Cano et al. designed epigallocatechin-3-gallate (EGCG) and ascorbic acid (AA) dual drug-loaded PEGylated Poly Lactic-Co-Glycolic Acid (PLGA) nanoparticles to improve the stability of EGCG by enhancing the bioavailability and effectiveness in the AD model. They concluded that nanoformulations of EGCG/AA nanoparticles (NPs) have a unique property to be developed as a safe and effective treatment of AD (Cano et al. 2019). In an interesting study, the neuroprotective potential of EGCG was explored using surface plasmon resonance imaging (SPRi) of Aβ aggregation. Based on the above findings, they suggested SPRi asone of the promising tools for screening the neuroprotective effects of new compounds (Cheng et al. 2013).

In a different study, Engel et al. showed EGCG amyloid inhibitor activity. They demonstrated that in contrast to its behavior in a bulk environment, EGCG has a strong potential to prevent hIAPP amyloid fibril formation at the phospholipid interface (Engel et al. 2012). In another study, the neuroprotective effect of EGCG in contrast to some other selective bioactive compounds was investigated against Aβ fibril formation and neuronal cell death in H_2O_2 developed pro-oxidant PC12 cells. Based on the findings of in vitro cell viability results and ROS assays, the authors concluded intense neuroprotective activity of EGCG (Harvey et al. 2011). In another study, Mori et al. investigated the combinatorial effect of EGCG and ferulic acid in the AD mice model.

Furthermore, combination treatment reduces neuroinflammation, oxidative stress, and synaptotoxicity. Authors concluded that using plant-derived phenolics, EGCG, and ferulic acid could serve as a promising therapeutic strategy to treat AD (Mori et al. 2018). Similarly, Lee et al. demonstrated the neuroprotective potential of EGCG against β-amyloid-induced cognitive dysfunction. The results of α-, β-, and γ-secretase assay demonstrated the $A\beta_{1-42}$ level reduced in the hippocampus and cortex region of the brain. Furthermore, Western blot results also illustrated the substantial reduction in signal conduction of kinase, and nuclear transcription factor (NF-kB) extracellular pathways were involved in apoptotic cell death induced by $A\beta_{1-42}$ (Lee et al. 2009). In another study, Smith et al. developed nanolipidic particles to improve the bioavailability and α-secretase inducing ability of polyphenol EGCG. Nanoformulations of EGCG exhibited significant α-secretase promoting activity in SweAPP N2a cells. In vitro results confirmed that this novel formulation of EGCG would be a promising approach to use for AD treatment (Smith et al. 2010).

Similarly, Zhang et al. prepared EGCG selenium nanoparticles coated with tet-1 peptide to stabilize and reduce cytotoxicity. Furthermore, in vitro results exhibited that both SE-EGCG- and Tet-1-EGCG-Se-coated nanoparticles could label Aβ fibrils with a high affinity and Tet-1 peptides promisingly improved the cellular uptake of Tet-1-EGCG-Se coated in PC12 cells in comparison to NIH/3T3 cells. So,

the anti-AD results of various studies strongly recommended that Tet-1-EGCG@Se was a novel therapeutic candidate for labeling and disaggregating Aβ fibrils (Zhang et al. 2014).

4.5 Baicalein and Berberine in AD

In a recent study, Chen et al. investigated that baicalein flavone has the potential to suppress the $A\beta_{1-42}$ protein-induced Alzheimer-like pathophysiological changes and cognitive dysfunction in the AD mice model. The findings of in vitro assays, immunohistochemistry, and Western blot demonstrated that baicalein possesses a strong neuroprotection potential to attenuate the $A\beta_{1-42}$-related pathological complications and memory (Chen et al. 2015). In another similar study, authors elucidated baicalein's neuroprotective effect on $A\beta_{1-42}$-induced cognitive dysfunction, Oxidative stress, apoptosis, and histopathological studies proved the significant neuroprotective role of baicalein in Aβ-induced hippocampus injury. Furthermore, results of the TUNNEL assay investigated the reduction in oxidative stress-induced cell death treated with baicalein. Hence, based on the above-accumulating evidence, the authors indicated baicalein as an effective therapeutic agent to treat AD (Ding et al. 2015). In a different study, Choi and colleagues aimed to develop an effective therapeutic candidate against Alzheimer's using a combination of flavonoids, baicalein, and daidzein to explore synergistic estrogenic and neuroprotective response using MCF-7 breast and PC12 neuronal cells. They further showed the synergistic activity of these two flavonoids. Finally, the authors concluded that daidzein and baicalein strongly potentiate the attenuation of $A\beta$ aggregation, and in the future, it could become a beneficial therapy against the treatment of Alzheimer's disease (Choi et al. 2013). Gu et al. aimed to investigate the protective role of baicalein against synaptic plasticity and cognitive dysfunction in a mouse model of Alzheimer's diseases. In vitro studies examined the effect of baicalein on $A\beta_{1-42}$ oligomer impaired long-term potentiation (LTP), which was investigated by electrophysiological methods. They also evaluated that baicalein significantly reduces the activity of 12/15 lipoxygenase (12/15LO) and glycogen synthase kinase 3β (GSK3β); β-secretase enzyme levels and concentration of total Aβ also block the phosphorylation of tau in APP/PS1 mice (Gu et al. 2016). Additionally, Xiong and colleagues elucidated baicalein's neuroprotective potential to attenuate Aβ-induced microglial cell activation through the Janus kinase/signal transducer and activator of transcription (JAK2/STAT3) signaling pathway. Both in vitro and in vivo studies showed the neuroprotective properties through anti-inflammatory, anti-proliferative effect through the JAK2/STAT3 signaling pathway, which revealed the new means to cure Alzheimer's disease (Xiong et al. 2014).

Another study aimed to elucidate Baicalein's inhibitory effect against hydrogen peroxide production and oxidative stress produced due to Aα aggregation in SH-SY5Y cells. Finally, based on experimental investigations, the authors concluded that baicalein possesses a strong ability to attenuate Aα aggregation.

Thus, it could act as a potential therapeutic agent to prevent the progression of neurodegenerative diseases such as AD (Fei Yina et al. 2011).

In a recent study, the authors demonstrated baicalein's ability to diminish the β-amyloid activity and to elevate the nonamyloidogenic APP processing in AD transgenic mice. In vitro and in vivo results evidenced that this flavonol improved the nonamyloidogenic processing of APP and was beneficial in reducing Aβ synthesis and cognitive impairment (Zhang et al. 2013).

Zhao et al. aimed to investigate in the AD model the combined effect of baicalein with ginsenoside Rb1 on the differentiation and proliferation of neural stem cells (NSC). Immunohistochemistry examinations indicated the significant increase in the percentage of NSCs, astrocytes, and neuronal cells in ginsenoside Rb1c and baicalein treated cells. In the end, the authors demonstrated the neuroprotective potential of combined ginsenoside Rb1 and baicalein therapeutic agents in AD treatment (Zhao et al. 1678). Asai and fellows aimed to elucidate the potential of berberine to inhibit Aβ secretion, which resulted in a change in the processing of Alzheimer's APP. They have shown that the APP-H4 neuroglioma cells (APP_{NL}-H4 cells) exhibited a significantly reduced level of Aβ without inducing any cytotoxicity and alteration in cell morphology. Therefore, based on these findings, the authors suggested that berberine could be a drug of choice in treating AD (Asai et al. 2007). In another similar study, berberine chloride's potential to improve cognitive dysfunction and anti-inflammatory response through upregulation of interleukin-1beta and nitric oxide synthase expression in an AD rat model was investigated. Findings on real-time polymerase chain reaction (RT-PCR) and immunohistochemistry analysis evidenced enhanced cognitive functions and anti-inflammatory activity (Zhu and Qian 2006).

In a recent study, berberine's potential against the cognitive experimental model of intracerebroventricular streptozotocin (ICV-STZ)-induced sporadic Alzheimer's-like dementia was investigated. Diverse in vitro and in vivo assays confirmed the neuroprotective behaviour of berberine against neurodegenerative conditions (Oliveira et al. 2016). In a similar kind of study, Durairajan et al. examined berberine's potential to improve β-amyloid pathology, gliosis, and memory dysfunction using the TgCRND8 transgenic mouse model (Durairajana et al. 2012). Another similar study aimed to investigate the improved memory dysfunction and antioxidative and anti-neuroinflammation potential of berberine (BBR) in APP/PS1 mice. Experiments showed that BBR could strongly inhibit the NF-κB signaling pathway and oxidative stress involved in neuroinflammation, resulting from hyperphosphorylation of tau proteins. Hence, further investigations about neuroprotective mechanisms of BBR might provide sufficient evidence as novel strategies for AD treatments (He et al. 2017).

Hussein et al. explored the neuroprotective role of berberine to counteract environmental heavy metal-induced Alzheimer's-like pathology in an experimental model of AD rat. In silico and docking studies proved that BBR significantly inhibited enzymes like acetylcholinesterase (AChE), cycyclooxygenase-2 (COX-2), and tumor necrosis factor-alpha converting enzyme (TACE) and

decreased the level of AChE expression in brain tissues. Additionally, ELISA measurement also confirmed the anti-inflammatory and antioxidant response via an elevated level of $A\beta_{42}$. Thus, the authors advocated the ability of berberine to protect against various inflammation and stress-induced neurodegenerative diseases and its application as a therapeutic agent to cure Alzheimer's-like disease (Hussain et al. 2018).

In another recent study, berberine's role was investigated to inhibit AChE, BChE, and two isoforms of monoamine oxidase (MAO) in Alzheimer's disease (Ji and Shen 2012). Molecular docking studies examined the close resemblance between in silico binding of berberine with AChE, BChE, and MAO. Moreover, further investigation demonstrated that significant forces involved in ligand-receptor interactions were the hydrophobic surface of berberine and neighboring hydrophobic residues. However, electrostatic interaction between the cationic surface of berberine and neighboring residues also participated but not in all of the above enzymes. Finally, the authors enlightened the molecular basis of the inhibitory impact of berberine against different enzymes involved in AD pathogenesis (Ji and Shen 2012).

A study conducted by Jiaa et al. aimed to explore the potential of berberine to inhibit the production of Aβ-induced inflammatory response in primary microglia and BV2 microglia cells through blocking of signaling pathways of nuclear factor-kappaB and mitogen-activated protein kinase. ELISA test results exhibited a significant reduction in Aβ-stimulated interleukin-6 (IL-6) and monocyte chemotactic protein-1 production in a concentration-dependent manner. Similarly, RT-PCR and Western blot analysis confirmed that berberine could strongly inhibit nuclear factor-kappaB (NFκB) and mitogen-activated protein kinase (MAPK) signaling pathway stimulation. Finally, the authors suggested berberine to be an important candidate for designing various strategies to treat neurodegenerative diseases like AD (Jiaa et al. 2012).

Liu et al. aimed to investigate the role of berberine to improve axonal transport defect and Calyculin-A-induced axonopathy in neuroblastoma-2a (N2a) cells. MTT assay exhibited the significant protection of berberine-treated cells against CA-induced toxicity as well as hyperphosphorylation of tau and neurofilaments (NFs). Additionally, berberine restored the activity of protein phosphatase 2A (PP-2A) by reversing the phosphorylation of the catalytic subunit of PP-2A and reduction in the level of SOD. So, based on the comparative analysis of berberine treated and untreated cells, it was suggested to use berberine as a therapeutic drug to treat AD (Liu et al. 2014).

In a recent study, Lohan et al. aimed to develop berberine (BBR)-loaded surface decorated multi-walled carbon nanotubes (MWCNTs) to manage AD. They validated the significant uptake of BBR-loaded MWCNT formulations through a confocal examination on SH-SY5Y cell lines. Further, pharmacokinetic analysis in rats elucidated the promising drug absorption in plasma and brain tissues. Moreover, the results of Morris Maze studies revealed a significant improvement in cognitive impairment and memory performance. Additionally, biochemical estimation indicated a significant reduction in oxidative stress-induced AD-like conditions.

So, above findings suggested the potential of BBR-loaded polysorbate/phospholipid coated MWCNTs in the management of AD (Lohan et al. 2017).

4.6 Quercetin in AD

In a recent study, in a triple transgenic Alzheimer's disease (3xTg-AD) mouse model, Paula et al. conducted a study to examine the role of chronic administration of oral quercetin on markers of neurodegeneration, cognitive behavior, and emotional deficits. This chronic treatment reduced the β-amyloidosis and tauopathy in the hippocampus and amygdala. They further showed that quercetin protects neuronal cytotoxicity, oxidation of protein, peroxidation of lipid, and Aβ-induced apoptosis. In the end, the authors concluded that quercetin might lead to delayed progression of histological hallmarks observed in AD patients (Paula et al. 2019).

Recently, Mani et al. induced AD in wild adult zebra fishes administering aluminium chloride via the intraperitoneal route. Behavioral and biochemical analyses were then performed which showed a reduction of oxidative stress and improved cognition. They also performed target identification, gene enrichment studies, and molecular docking studies. The results depicted the protective effects of quercetin on the AD model (Mani et al. 2018). A similar study by Ansari et al. evaluated quercetin's dose-response pattern and showed that quercetin protects against Aβ toxicity by reducing oxidative stress at lower doses. Bioinformatics studies were applied to know the binding sites of AChE. One of the binding sites was used for molecular docking of quercetin with AChE. Finally, the authors suggested that quercetin might act as an AChE inhibitor (Ansari et al. 2009). Quercetin's impact on the inflammatory response was explored by Vargas-Restrepo and colleagues in the CA1 area of the hippocampus in a 3xTg-AD male and female mice model. In this study, histological and biochemical experiments were performed. And it was observed that the proinflammatory response in the CA1 hippocampal region of aged 3xTg-AD mice was lowered along with GFAP, inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX-2) immunoreactivity, and interleukin 1β (IL-1β) in hippocampal lysates with the quercetin administration. Authors hypothesized that quercetin decreases the tauopathy by regulating IL-1β/p38 MAPK activation, ultimately leading to enhanced cognitive performance (Vargas-Restrepo et al. 2018).

Anticholinesterase and antioxidative activity of quercetin and its glycosylated form rutin was explored in an interesting study. In vitro studies depicted the inhibition of AChE and BChE activities with inhibition of Fe^{2+}-induced peroxidation of lipid in homogenates of rat brain. Apart from this, quercetin portrays better radicals scavenging and Fe^{2+}-chelating abilities than rutin. The authors further proved better quercetin activity through the IC_{50} values (Ademosun et al. 2016).

In an animal model of AD, in the hippocampus, Tong-Un et al. assessed the effects of nasal route administration of quercetin liposomes on cognitive behavior and biochemical markers of oxidative stress, SOD, catalase, glutathione, and MDA. This nasal quercetin liposome administration significantly improved memory

impairment by inhibiting the oxidative damage of the hippocampus. This could be related to the decreased MDA level and improved level of SOD, catalase, and glutathione (Tong-Un et al. 2010).

Ashrafpour et al. assessed acquisition and retention of spatial memory by quercetin in a rat model of AD. The results showed that intracerebroventricular (ICV)-STZ AD groups exhibited significant impairment in the acquisition and retrieval of spatial memory as compared to the control group. In the AD groups, training trials showed considerable downfall in escape latency. The authors concluded that quercetin acted as a spatial memory enhancer in ICV-STZ-induced AD rats (Ashrafpour et al. 2015). In another work, quercetin's role on cytotoxicity and cognitive impairment caused by Aβ-peptide in mice was explored. In this study, quercetin inhibited the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical activity and protected PC12 neuronal apoptosis induced by the treatment of Aβ (Li et al. 2017). Kim et al. demonstrated the protective effect of quercetin and quercetin-3-b-D-glucoside (Q3G) in the T-maze and object recognition test, as compared with $A\beta_{25-35}$-injected control mice; administration of quercetin and Q3G improved memory and cognitive function. Compared to the Q3G administered group, the quercetin group exhibited enhanced protective effects from long-term spatial memory and learning ability impairments. Besides, in the brain of $A\beta_{25-35}$-injected control mice, peroxidation of lipid and formation of nitric oxide (NO) was significantly increased. In the end, the authors suggested quercetin could be a better option for the management of AD (Kim et al. 2016).

Recently, Molaei et al. reported an interesting work to assess quercetin's synergic effects (as chemical treatment) and exercise (as physical treatment) on AD-induced learning and memory impairment. When the treatment was completed, the results depicted that streptozotocin (STZ) in rats led to the impairment of spatial memory and enhanced hippocampus oxidative stress. However, pretreatment with exercise or quercetin injection enhanced spatial memory and oxidative stress caused by STZ injection, the combination of quercetin and exercise pretreatment was more efficacious (Molaei et al. 2020). Aliaga et al. investigated the anti-amyloidogenic and antioxidant properties of quercetin. In this study, quercetin inhibited the formation of Aβ fibrils and disaggregated Aβ fibrils.

Furthermore, quercetin decreased almost entirely ROS generation in H_2O_2 treated APPswe cells. Moreover, intracellular GSH content and redox status were improved and diminished the index of lipid peroxidation as compared to the control APPswe cells after quercetin treatment (Jiménez-Aliaga et al. 2011). In another study, in human neuronal SH-SY5Y cells, quercetin neuroprotective effects were investigated against H_2O_2-induced apoptosis. In a quercetin concentration-dependent manner, H_2O_2-mediated cytotoxicity and lactate dehydrogenase (LDH) release were suppressed. Additionally, in SH-SY5Y cells, quercetin reduced Bax gene expression and enhanced the level of Bcl-2 gene. Moreover, activation of the caspase cascade which leads to DNA fragmentation ultimately responsible for apoptosis was also inhibited effectively by quercetin. Thus, quercetin exhibited significant neuroprotective activity to prevent neurodegeneration progression induced by oxidative stress (Suematsu et al. 2011).

Heo et al. investigated the protective effects of quercetin on hydrogen peroxide, and a significant decrease in cell viability was observed. However, preincubation with quercetin and vitamin C protected H_2O_2-induced toxicity in PC12 cells in a dose-dependent manner. As it is already known that oxidative stress increases neuronal cell membrane breakdown, lactate dehydrogenase and trypan blue exclusion assays were performed. The results showed that quercetin decreased oxidative stress-induced neuronal cell membrane damage higher than that of vitamin C. The authors concluded that quercetin contributed significantly to cells' neuroprotection from oxidative stress-induced stress neurotoxicity (Heo and Lee 2004). Nakagawa et al. assessed the role of long-term quercetin intake on memory recall in aged wild-type mice by using contextual fear conditioning. They also studied whether memory recall was affected by the administration of quercetin-rich onion powder in early-stage AD patients. Later on, in vivo analysis indicated that aged mice fed with quercetin-containing diet showed improved memory recall. Additionally, the Revised Hasegawa Dementia Scale was used to identify memory recall in early-stage AD patients, which was significantly improved by the intake of quercetin-rich onion powder for 4 weeks compared with the intake of control onion powder (Nakagawa et al. 2016).

The protective effect of quercetin and its glycosides, rutin and quercitrinon reactive oxygen species (ROS)-dependent (H_2O_2) and -independent (chemical anoxia) apoptosis in rat glioma C6 cells was investigated by Chen et al. Authors found that incubation of C6 cells with quercetin, but not rutin or quercitrin, protected C6 cells from cytotoxicity induced by H_2O_2 and chemical anoxia as shown by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and LDH assays. Quercetin, rutin, and quercitrin dose-dependently inhibited DPPH radicals' production in vitro as demonstrated by anti-DPPH radical assay. On the other hand, DNA damage induced by OH radicals was prevented by quercetin (but not rutin and quercitrin), as shown by plasmid digestion assay. Altogether, this study concluded that quercetin showed an inhibitory effect on both ROS-dependent and ROS-independent apoptosis, and induction of HO-1 protein expression was also identified (Chen et al. 2006).

In separate work, in the AD *Drosophila* model, Kong et al. showed the impact of quercetin and explored the underlying mechanisms. This study showed that quercetin might restore the gene expression agitated by an accumulation of Aβ. Furthermore, it was also shown that cyclin B RNAi in the brain could ameliorate AD phenotypes. Altogether, neuroprotective effects of quercetin were significantly exhibited by this interesting study (Kong et al. 2016).

Ginkgo biloba extract EGb761 tends to protect against Aβ-induced neurotoxicity, but the mechanisms remain unknown. To elucidate this further, Shi et al. tested the effects of EGb761 and its two important constituents, quercetin and ginkgolide B, on the cytotoxic action of $A\beta_{1-42}$ with human neuroblastoma SH-SY5Y cells. Authors demonstrated that through c-jun N-terminal kinase (JNK), extracellular signal-regulated kinase 1/2 (ERK1/2), and Akt signaling pathways, EGb761 blocked the $A\beta_{1-42}$-induced cell death, ROS accumulation, and mitochondrial dysfunction. It

was also shown that the same signaling pathway also demonstrated that quercetin and ginkgolide B might be involved in the inhibitory effects of EGb761. Ginkgolide B also improved the functions of mitochondria, but quercetin failed to do so. Individual EGb761 components showed the direct mechanisms underlying the neuroprotective effects of EGb761 (Ihl et al. 2011).

4.7 Clinical Trial of Some Natural Compound in AD

Ihl et al., in a clinical trial, revealed that *Ginkgo biloba* extract EGb 761 increased the baseline in primary outcomes Erzigkeit's short syndrome test (SKT) and neuropsychiatric inventory total score. Simultaneously, SKT was found to be decreased, and no change was observed in NPI score after placebo once-daily dose treatment for 24 weeks in 410 patients. Interestingly, extract EGb 761 showed significant results compared to placebo in secondary outcome measures (Ihl et al. 2011). The same group tested the efficacy of EGb 761 in AD and vascular dementia in 404 outpatients aged 50 years or above and reported enhanced therapeutic effects (Ihl et al. 2012). Additionally, Herrschaft et al. reported improved SKT total score and NPI composite score in patients treated with EGb 761 and placebo. Simultaneously, most of the secondary efficacy variables provided better results with a once-daily dose of 240 mg of EGb 761 (Herrschaft et al. 2012). Most surprisingly, Villas and colleagues demonstrated that participants aged 70 years or above who were given one dose of placebo and EGb 761 for 5 years were unable to show any protective action in lowering AD's progression (Vellas et al. 2012).

Furthermore, Gavrilova et al. summed up that long-term exposure to *Ginkgo biloba* extract was considered to be beneficial in improving cognitive performance in patients with mild cognitive impairment (MCI) and neuropsychiatric symptoms (NPS) with no severe adverse reaction reported (Gavrilova et al. 2014). Meanwhile, Rafii et al. indicated that Huperzine A 200μg BID did not exert any change in Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) at 16 weeks of primary analysis, while 400μg bis in die (BID) given in secondary analysis showed enhancing effect in ADAS-Cog. Still, the effect got declined in the placebo group at 16 weeks (Rafii et al. 2011). In this regard, Yang et al. confirmed the similar action of Huperzine A in improving cognitive function with no significant adverse effect reported in AD patients (Yang et al. 2013). Moreover, Ringman and colleagues pronounced that placebo and curcumin C3 complex treated group showed some adverse effects after 24 weeks of trial. However, they were unable to determine the sufficient efficacy of the drug due to low plasma level (Ringman et al. 2012). In a study, Nelson et al. indicated that bryostatin increased BDNF and PSD-95, MMSE score at 3 h, and peripheral blood mononuclear cells-protein kinase C epsilon (PBMCPKCε) level within 1 h after IV infusion and concluded that this drug was well tolerated in patients (Nelsona et al. 2017). A Phase-II trial by Farlow et al. also reported similar results and suggested bryostatin was considered safe and effective as compared to the placebo-treated participants (Farlow et al. 2018). The

study performed by Turner et al. revealed the reduced CSF Aβ40 and plasma Aβ40 levels after placebo treatment.

Additionally, magnetic resonance imaging (MRI) detected that resveratrol treatment decreased brain volume and increased ventricular volume at 52 weeks compared to a placebo-treated group (Scott Turner et al. 2015). In addition to this, Zhu et al. conducted the study with no significant difference in scores obtained from resveratrol-, glucose-, and malate-treated patients. Although low-dose resveratrol was safe and well tolerated, the study did not prove effective in stopping disease progression (Zhu and Grossman 2018). Simultaneously, Chang et al. implied that memantine's efficacy was enhanced in combination with tenuigenin and β-asarone. They observed an increase in change scores after 12 weeks of treatment which would be beneficial in treating moderate-to-severe Alzheimer's disease mainly in 60–74-year-old patients (Wenguang and Junfang 2018).

4.8 Corelation Between Microbiota Activity and Polyphenolic Compounds

As we know, polyphenols in the diet are necessary to nurture one's health, especially the gut, and they do so by prompting the growth of particular bacterias and inhibiting the growth of unwanted bacterias. Through recent advancements in the field of science and technology, there are chances for a better understanding of the interaction between dietary phenols and gut microbiota (Popa et al. 2017). This hypothesis has further been supported by Cardona et al. (2013) and Tomás-Barberán et al. (2016). Additionally, Cardona F et al. briefed that microorganisms convert polyphenols into active metabolites, and hence the changes in gut microbiota have the tendency to affect the polyphenol activity (Cardona et al. 2013). Moreover, for an in-depth knowledge of this relationship, metagenomic and metabolomic studies should be conducted (Cardona et al. 2013).

4.9 Conclusion

In conclusion, we can say that several natural compounds like green tea, epigallocatechin gallate, baicalein, berberine, quercetin, *Ginkgo biloba*, and Huperzine A exhibit potent neuroprotective activity in AD treatment. These natural compounds can stop AD progression by acting on amyloid and tau pathology (Fig. 4.1). Clinical trials also show the efficacy of some of the common natural products like *Ginkgo biloba* and Huperzine A. Further studies will be needed to explore additional bioactive compounds present in these natural products for their AD treatment role.

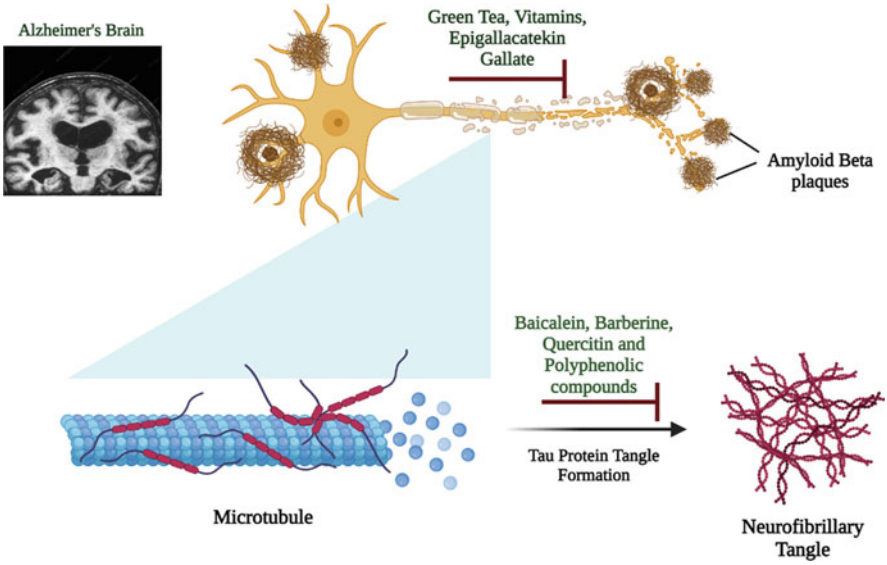

Fig. 4.1 Some natural compounds like green tea, vitamins, and epigallocatekin gallate inhibiting beta-amyloid plaque formation and other natural compounds like baicalein, barberine, quercetin, and polyphenolic compounds inhibiting neurofibrillary tangle formation in Alzheimer's disease pathology

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Mapping a Link Between Mercury Toxicity and Alzheimer's Disease

5

Swati Kundu

Abstract

Alzheimer's disease (AD), the most common form of dementia, poses a threat to the elderly worldwide. During AD progression, neurons' structural and functional features are affected by the accumulation of amyloid beta-peptide (Aβ) and tau protein. This study investigates the role of environmental toxicants, mercury, accelerating AD symptoms, and natural compounds' therapeutic potential in preventing AD. Mercury caused aggregation of Aβ protein, thus establishing a direct link between AD's mercury toxicity and pathogenesis. Natural compounds with antioxidant and anti-inflammatory properties, namely, curcumin, carvacrol, eugenol, and linalool, can be used to treat AD. This study focuses on the environmental toxicants as a risk factor in AD's pathogenesis and provides a vision to look for natural compounds as therapeutics for AD treatment.

Keywords

Alzheimer's disease · Carvacrol · Curcumin · Eugenol · Mercury · Natural compounds · Linalool

Abbreviations

Aβ	Amyloid beta protein
AD	Alzheimer's disease
APP	Amyloid precursor protein
BBB	Blood-brain barrier

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NFT Neurofibrillary tangles
NP Neuritic plaques
PS Presenilin
ROS Reactive oxygen species

5.1 Introduction

A neurodegenerative disease where an irreversible and progressive loss of memory occurs is termed Alzheimer's disease (AD). Symptoms usually go unnoticed during the infection stages, and the symptoms are prominent in later stages when there is a subtle decline in cognitive function (Braak et al. 2011). This affects individuals' daily activities and ends in fatality. It usually hits at the age of >60 years; however, this is not mechanistically linked to brain ageing (Nelson et al. 2011).

The prevalence rate of AD has shown a peak in the last 10 years and has become a known cause of dementia in Western countries (Alzheimer's Disease International 2019). Its age-wise distribution in European countries is shown in Fig. 5.1. An estimate reveals that AD would be affecting approximately 152 million population by 2050 across the world (Alzheimer's Disease International 2019). Unsurprisingly, AD has gradually become one of the major reasons for the rising number of deaths in the elderly population, just after cardiovascular diseases and cancer (Alzhemier's Association 2020). Figure 5.2 illustrates the death rate of patients suffering from AD across various countries. Due to this disease's rising trajectory, low survival rate, and substantial financial burden on the family, it becomes imperative to unravel the

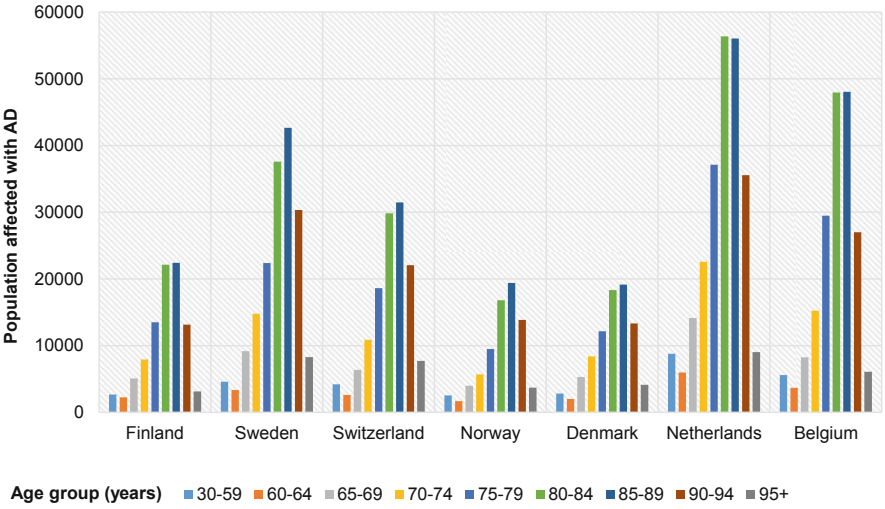


Fig. 5.1 Age-wise distribution of population affected with AD in Europe (World Health Organization 2020)

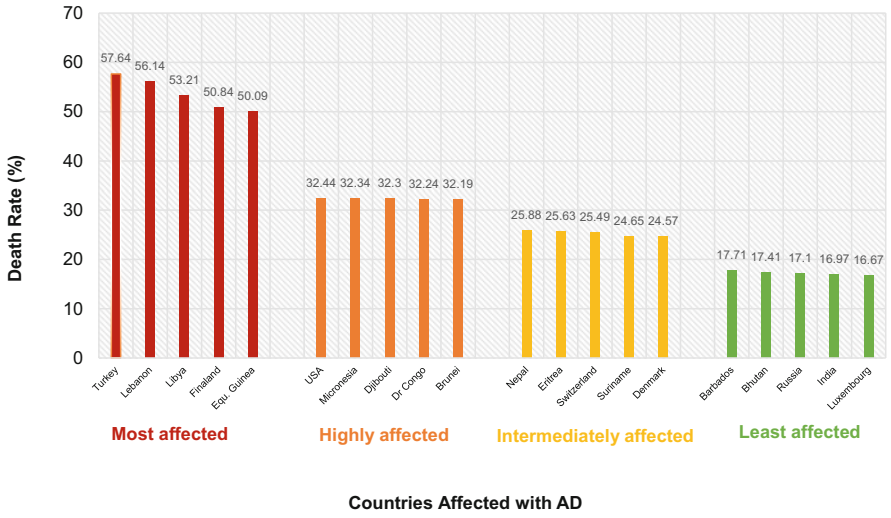


Fig. 5.2 The death rate of top five countries from most, highly, intermediately, to least affected with AD categories (World Health Organization 2020)

causes and potential therapies to control the disorder. This chapter will review AD's pathophysiology, how it gets affected by environmental factors, and the potential of natural therapeutics to prevent AD symptoms.

5.1.1 Functional Alteration in the Brain During AD

A healthy human brain has about a hundred billion neurons, a specialized cell designated to transmit information in chemicals from one to the other. Their extensions form a connection known as synapses, where this chemical transfer occurs. This rapid transfer through the synapses generates a cellular basis of memories, thoughts, sensations, emotions, and skills. Any changes in the structural form or protein accumulation inside/outside the neurons lead to cognitive capability loss. During the progression of AD, risk factors, namely, amyloid precursor protein (APP) and presenilin (PS), are known causes for early onset; however, apolipoprotein E allele 4 (APEA4) mutation is a high risk factor for late-onset AD (Koffie et al. 2012; Meraz-Ríos et al. 2014). APP, a single-pass transmembrane protein, is highly expressed in the brain which is cleaved via either α- and γ-secretases or β- and γ-secretases and generates amyloid beta-peptide (Aβ) (Sadigh-Eteghad et al. 2015).

Moreover, the proteolytic function of γ-secretase is regulated by PS (Ridge et al. 2013). APEA, a dominant cholesterol and lipid carrier in the brain, regulates Aβ aggregation and clearance in the brain (Liu et al. 2013a). An increased concentration of Aβ impairs blood flow within the cerebral structure and speeds up neuronal dysfunction. Additionally, an increased reactive oxygen species (ROS) generation and mitochondrial damage are reported by the risk mentioned above that enhance

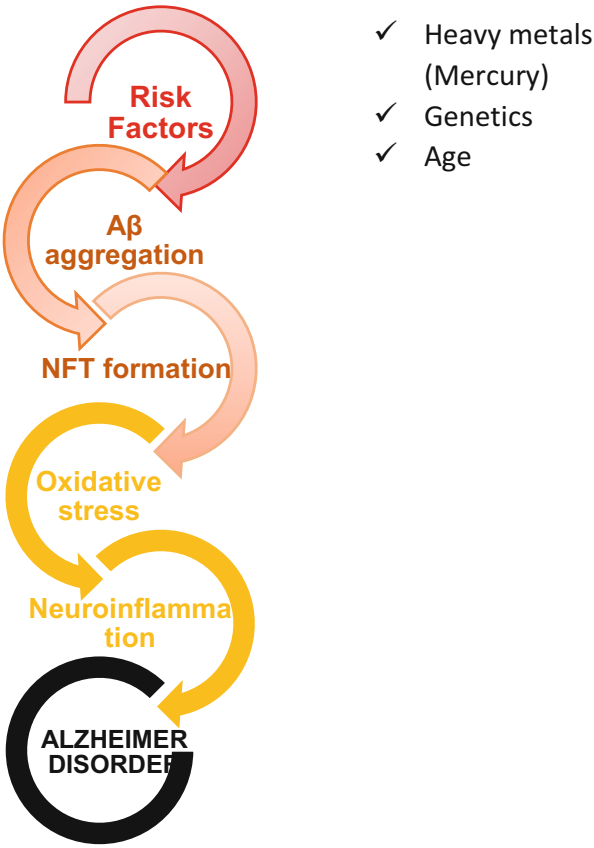


Fig. 5.3 Schematic representation of AD development

AD's neurodegenerative process (Meraz-Ríos et al. 2014). A sequential progression of AD is shown in Fig. 5.3.

In AD, accumulation of Aβ acquires a *β-sheet structure which* forms a spherical deposit called neuritic plaques (NP) (Sakono and Zako 2010). It is a 39–42 amino acid peptide consisting of fibrillary core and microglia, astrocytes, and neurites surrounding the core. These NPs are deposited outside the neurons and interfere with neuron communication at the synaptic junction. This amyloidosis process also leads to the hyperphosphorylation of the microtubule-associated protein called tau protein (Li et al. 2016). It leads to the breakdown of microtubules and neuronal skeleton resulting in the accumulation of flame-shaped neurofibrillary tangles (NFT) which promote neuroinflammation. The Aβ fragments are deposited outside the neurons causing interference in their communication, whereas tau protein deposits inside the neurons and blocks transmission of essential nutrients to the brain (Alzhemier's Association 2020).

5.1.2 Challenges in the AD Treatment

Limited understanding of brain complexity poses a daunting challenge in the treatment of neurodegenerative disorders, including AD. A semipermeable membrane of the brain, the blood-brain barrier (BBB), limits drug penetration, which is the foremost cause for failure of proposed drugs in their preclinical trials for AD (Pardridge 2009). Another hurdle during clinical trials for AD is the enrollment of patients (Watson et al. 2014). This may be due to the poor public awareness and high risk involved in the trials. Crucially, there is no standardized effect on the general population, and its resultant effectiveness varies from one individual to the other (Watson et al. 2014). Some drugs, namely, rivastigmine, galantamine, donepezil, memantine, memantine combined with donepezil, and tacrine, have been approved by the US Food and Drug Administration (Alzhemier's Association 2020). However, these drugs do not entirely cure AD but are effective over the short term. Additionally, we need to emphasize the risk factors, including environmental causing AD.

A link between environmental factors and the development of AD is well established (Killin et al. 2016). Although factors like age, family history, prevailing health conditions, etc. cannot be changed, environmental factors can be assessed carefully to reduce the risk of cognitive decline. These factors include heavy metal toxicity, which is reported to cause systemic alterations when exposed to their threshold concentration (Bakulski et al. 2020). Among heavy metals, mercury seems to be the most hazardous one as it does not have any physiological function and excretory mechanism in humans. Therefore, a longer duration of mercuryexposure leads to its accumulation in nervous tissue.

5.1.3 Role of Mercury Toxicity

Historically, mercury toxicity has resulted in two major pandemics—the Minamata Bay disaster and the Iraq incident. These incidents gave a clear picture of the neural damage caused by mercury ingestion causing sensory, motor, and visual disturbances (Harada 1986). The chemical form and dose of mercury to which the human system gets exposed define its toxicity. As per the US Environmental Protection Agency, the recommended reference blood concentration of mercury is 5.8 ng/mL; concentrations below this level are safe (Choi et al. 1981). Its vapor form (elemental) makes it easily absorbable by biological tissue such as the respiratory system. Since there is no mercury physiological function in humans, 80% of mercury gets accumulated into tissues and cells in its oxidized form of Hg^{2+} (inorganic form). Now, this Hg^{2+} form can bind to the sulfhydryl groups of thiol, hereby altering cysteine-containing proteins (Rooney 2013). This results in the variation in these proteins and, therefore, inhibiting their enzymatic function.

Mercury (organic form) can cross the blood-brain barrier (BBB) by binding to the thiol group and gets converted into an inorganic form in the neurons and glial cells (Cariccio et al. 2019). In the brain, mercury is reported to interact with numerous

targets involved in various cellular functions and, therefore, interfere with the brain's structural stability and functionality. The high affinity of mercury for thiol and selenol groups leads to depleting intracellular antioxidants, causing inhibition of antioxidant enzyme activity (Wagner et al. 2010). This results in a redox imbalance causing oxidative stress. Also, dysregulation of calcium stores results in calcium overload in the brain which elicits mitochondrial permeability transition pore opening leading to ROS overproduction (Roos et al. 2012). A resultant alteration in chemical signals from the presynaptic membrane occurs, causing postsynaptic receptor functions (Castoldi et al. 2001).

In AD, mercury binding to neuronal microtubules via thiol group blocks their assembly and causes tubule disintegration (Siblerud et al. 2019). The structural formation of neurons, an important factor in its sustainability and survival, is stabilized by polymerization/depolymerization cycle of the cytoskeleton components—actin filaments (F-actin) and microtubules (β-tubulin). Mercury causes a change in β-tubulin; however, F-actin intensity remains unchanged (Xu et al. 2012). Another consequence of mercury toxicity is the inhibition of glutamate uptake a neurotransmitter by altering glutamatergic signaling in astrocytes (Aschner et al. 2000). This causes an increased glutamine synthase activity, and a sudden increase in glutamate release from the neuron occurs (Fuentes et al. 2001). Consequently, glutamate levels rise from 0.6 to 10μM at the synaptic cleft, which is a critical factor in the regulation of neural signaling (Bouvier et al. 1992).

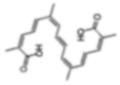
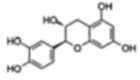
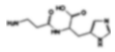
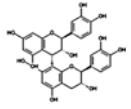
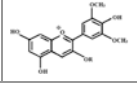
Taken together, environmental toxicants in the form of mercury directly accelerated the progression of AD symptoms by altering neural signaling.

5.1.4 Natural Compounds as AD Therapeutics

For ages, natural compounds hold prime importance for therapeutic use. Based on the fact, in my previous research, based on antioxidant and anti-inflammatory properties, I selected four natural compounds to study their effect on mercury toxicity (Kundu et al. 2014, 2016). All these four compounds show not only ameliorative but also prophylaxis effect against mercury in smooth muscle systems. Their action of mechanism against mercury toxicity makes them suitable candidates to study in AD. Some natural extracts are already in clinical trials to treat AD (Table 5.1), while some natural compounds (mentioned below) are in their preclinical trials that need to be investigated further in AD treatment.

(a) Curcumin is an active component of *Curcuma longa* L. plants. Its antioxidant and anti-inflammatory potential is known to act against oxidative stress caused during AD (Reddy et al. 2016). Curcumin has shown preventive actions against AD by counteracting its primary cause, i.e., Aβ aggregation, at IC50 = 0.8 **μ**M (Yang et al. 2005). A decrease in Aβ pathological aggregation has been reported by inhibiting PS-2 or accelerating its clearance through degrading enzymes (Wang et al. 2014). Furthermore, in vitro experiments showed that curcumin at 0–20 **μ**M reduced secretion of β- and γ-secretase, leading to improvements in

Table 5.1 Natural extracts in clinical trials for AD therapy

Natural extracts	Structure	Active component	Toxicity	Severity level of AD	Outcomes	Reference
Saffron oil		Crocetin, crocin, safranal	0.15 and 0.35 mL/kg, i.p.	Mild	Improved cognitive functions	Hosseinzadeh and Talebzadeh (2005), Gavrilova et al. (2014)
Green tea extract		Alkaloids and tannins	210 mg/kg	Severe	Improved cognitive function and memory	Arab et al. (2016), National Library of Medicine (2013)
Papaya		Alkaloids, tannins, antraquinone, cardenolides, steroids, saponins, phenolics	Data not available	Last stages	Decreased oxidative stress	Barbagallo et al. (2015)
Coconut oil	Due to flexibility, 3D structure is not available	Lauric acid and myristic acid	Data not available	Last stages	Improved cognitive functions	De la Rubia Orti et al. (2018)
Apple extract		Quercetin-3-galactoside, catechin, epicatechin, procyanidin, cyanidin-3-galactoside, coumaric acid, chlorogenic acid, gallic acid, and phloridzin	13,956 mg/kg	Moderate	No improvement in cognitive functions	Remington et al. (2010), U. S. National Library of Medicine (n.d.)
Blueberry extract		Phenolic compounds	Data not available	Initial stages	Improved learning ability	Krikorian et al. (2010)

learning and memory (Xiong et al. 2011). A clinical trial conducted to ascertain curcumin's side effects proved it a safe compound for AD patients (Baum et al. 2008). However, more clinical trials are needed to know the efficacy of curcumin in AD treatment.

(b) Carvacrol is an active component of thyme oil. A study shows the effectiveness of carvacrol against AD by alleviating cognitive impairments. This effect was mediated at 471.2 mg/kg of carvacrol which increased levels of Aβ and cholinergic hypofunction (Azizi et al. 2012). Carvacrol (IC50 = 0.063 **μ**M) also displays an inhibitory effect on acetylcholinesterase, resulting in the loss of its function (Jukic et al. 2007). An increased acetylcholine concentration in the brain leads to better neuron-neuron communication, which repairs the loss of cognitive function during AD. These studies highlight the natural therapeutic potential of carvacrol; however, detailed investigations can only summarize the clinical efficacy and potential sideeffects in the human system.

(c) Eugenol is an active compound of clove oil, cinnamon, and basil. In AD, eugenol at the concentration of 0.01 mg/kg has shown a reduced amount of amyloid plaques significantly in the hippocampus part of the brain (Taheri et al. 2019). This results in improved memory in AD rat models. Also, an increase in the activity of antioxidant enzymes (glutathione peroxidase and superoxide dismutase) and a decrease in the malondialdehyde content in the hippocampus area in the eugenol treated rats have been reported (Liu et al. 2013b). Eugenol has also shown its stabilizing effect for a native protein that delays the conversion of the native conformation into β-sheet assembled mature fibrils, preventing AD symptoms (Dubey et al. 2017).

(d) Linalool is an active ingredient of lavender oil. It showed a reversal of AD's histopathological hallmarks and subsequently restores cognitive functions in hippocampus and amygdala parts of the brain (Maria et al. 2016). The concentration used to study the effects was 25 mg/kg. It shows anti-inflammatory effects including a significant reduction in the levels of the pro-inflammatory markers—*p38 MAP Kinase*, nitric oxide synthase 2, cyclooxygenase-2, and *interleukin-1β*—and antioxidant effects including maintaining antioxidant enzyme (superoxide dismutase, glutathione peroxidase) activities and malondialdehyde levels and enhanced activity of acetylcholinesterase (Xu et al. 2017; Maria et al. 2016). This results in the reduction of extracellular β-amyloidosis, tauopathy, astrogliosis, and microgliosis, leading to AD's improved symptoms. Linalool showed therapeutic potential against AD, which makes it an ideal candidate for clinical investigations.

5.2 Summary

This review presents mercury toxicity as one of the significant risk factors humans face in terms of loss of brain function, leading to AD. Further experimental data may warrant a neural cascade affected with acute and chronic mercury exposure. My previous studies have established the prophylaxis and ameliorative role of natural

compounds against mercury toxicity which calls for a check of their potential role in AD considering mercury as a risk factor. In vivo and in vitro studies done with some of the natural compounds imply that treatment with curcumin, carvacrol, eugenol, or linalool may inhibit the pathological mechanism(s) responsible for the development of AD, including Aβ accumulation, oxidative stress, and neuroinflammation. If we keep a check on the mercury accumulation in our system and look for natural compound dosages which we should consume, it may open a new way in AD therapeutics.

Conflicts of Interest All the authors declare no conflict of interest.

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Drug Therapy of Alzheimer's Disease: Cholinesterase Inhibitors, NMDA Antagonists

6

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Abstract

Alzheimer's disease (AD) is one of the brain's progressive neuronal diseases named after Aloes Alzheimer, a German physician who first described it in 1906. AD is one of the most widespread forms of dementia, presenting one of the biggest healthcare challenges in developed countries. AD causes a reduction in cognitive function and language ability. Multi-target inhibitors have been developed as AD is a multifactorial disease. There is no effective treatment capable of slowing down disease progression. Recently, the primary focus of research is on novel pharmacotherapies. Several current drugs taken to treat the disease have repulsive side effects and new substitutes. There is no therapy for AD, but medicines are available that are designed to slow disease progression. Various studies have shown that some herbs may improve brain function; however, experimental data is limited to prove that they can treat AD. The objective here is to provide a systematic review of AD's factors, viz., environmental toxicity and genetic predisposition, and ongoing treatment strategies used to treat it. Additionally, this review presents the current status and future directions for developing novel drugs with pharmacological activity. Evidence about the use of medicinal herbs in treating AD and symptoms related to AD is discussed.

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Keywords

Alzheimer's disease · Environmental toxicity · Genetic predisposition · Treatment strategies · Medicinal herbs

6.1 Introduction

Alzheimer's disease (AD) comes under a broad category of neurodegenerative disorders (ND). The NDs are characterized by the progressive and irreversible loss of neurons from specific regions of the brain. The NDs also include Parkinson's disease (PD) and Huntington's disease (HD), where basal ganglia neurons are involved, and amyotrophic lateral sclerosis (ALS), where degeneration of spinal, bulbar, and cortical motor neurons are involved. In AD, there is a loss of hippocampal and cortical neurons resulting in disability of memory and cognition. AD is the most common cause of dementia. There is persistent memory loss combined with personality changes. The main risk factor for AD is age; AD affects 10% of the population above the age of 65 (Evans et al. 1989). In AD, the hippocampus and neocortex are most affected, but AD may also involve other brain regions (Arnold et al. 1991).

AD is the most important cause of dementia, accounting for 60–70% of cases. The sign of this dreadful disease deteriorates over time—from early lack of memory to regular degeneration in language, orientation, and behavior and delayed severe loss of memory and a few body functions till final death. The etiology of AD appears to be multifactorial. Genetic mutations in presenilin (PS1, PS2) and amyloid precursor protein (APP) genes, affecting a common pathogenic pathway in APP synthesis and proteolysis, cause early onset of familial AD, causing the production of amyloid β (Aβ) in excess (Wu et al. 2012). However, the cause of AD's late onset is inadequately understood, but it is believed that the leading risk factor is the involvement of genetics with several genes. Aging, apolipoprotein (Apo) E4 genotype, head trauma, and vascular conditions are other threats to the disease (Burns and Iliffe 2009). Both structural and functional abnormalities are involved in the pathophysiology of AD. Numerous injuries occur in the brain, including the appearance of senile plaques consisting of Aβ and neurofibrillary tangles containing phosphorylated tau as AD goes into the advanced stage and the substantial loss of synaptic profiles (Perl 2010). Significant oxidative stress and mitochondrial abnormalities are also observed in AD together with neuronal death. There is no cure for AD through a small number of treatments till now. FDA approved two categories of drugs for the treatment of AD patients according to the AD Medications Fact Sheet published by the National Institute on Aging. One is cholinesterase inhibitors for mild to moderate AD. In contrast, the other is used to treat moderate-to-severe AD and contains memantine, an antagonist against *N*-methyl-D-aspartate receptor (NMDAR), a receptor gated by the neurotransmitter glutamate.

The purpose of this chapter is to shed light on the factors associated with AD, viz., environmental toxicity and genetic predisposition, and current treatment strategies used to treat AD. Moreover, this chapter presents the current status and future directions for developing novel drugs with pharmacological activity, medicinal herbs in the treatment of AD, and the symptoms related to AD.

6.2 Environmental Toxicity and Genetic Predisposition

Some of the environmental agents including (1) toxic metals, (2) insecticides and pesticides, (3) industrial/commercial pollutants, (4) antimicrobials, and (5) air pollutants are all known to aggravate AD in vitro, in vivo and in clinical research. Aluminum (Campbell 2002) and lead (Basha et al. 2005; Shih et al. 2007) are known toxic metals that have been linked with many neurodegenerative diseases, including AD, which cause toxic effects to many organs of the human body. Copper and arsenic are other elements that disrupt the homeostasis of brain amyloid-β protein associated in experimental model systems (Baum et al. 2010; Singh et al. 2013). Chronic exposures to pesticides such as organophosphates (Kamel and Hoppin 2004), simultaneously with occupational exposure predominantly in agriculture, have been shown to lead to cognitive and psychomotor impairment and possibly to the progress of AD (Baldi et al. 2003). Behavioral changes were observed in murine neonates exposed to brominated flame retardants, which are readily absorbed by body fat, whereas adult mice exhibited impaired learning and remembrance (Viberg et al. 2003). The use of plasticizers like, bisphenol A and phthalates can cross the fetoplacental barrier to damage neurons (Zaman 2010). Neurodevelopmental disturbances and behavioral changes were observed using broad-spectrum antimicrobials, which are active ingredients of consumer products like soaps and toothpaste; however, direct evidence linking these to AD is missing (Barse et al. 2010; Veldhoen et al. 2006). Studies have been done on animal models, and epidemiological approaches have reported other evidence that link with the exposure to toxic metals (Sparks and Schreurs 2003; Thompson et al. 1988) and air pollutants that cause neurological symptoms, including AD. Significantly, most of the concerned environmental toxins are endocrine-disrupting chemicals that impair neurogenesis and cognitive function in brain development and affect the neurological function throughout human existence (Weiss 2007).

It remains unknown whether a single agent or combination of environmental factors contributes to AD's onset and progression. Further research is in progress to endow with new insights into possible mechanisms to identify environmental risk factors and strategies to lessen harmful exposures contributing to AD.

AD has a very strong root in genetics, whose classification has become an essential part of hard work to know its pathology. For the last 10 years, AD risk has been linked to more than 40 genes. Genetic data has shed new light, particularly the main role of microglia and the pathogenesis of AD. However, further various genetic studies are essential as our information of the genetics of AD is not sufficient. Families with a high incidence have been identified and showed some evidence of

the disorders' pathogenesis, although most AD cases are sporadic. Mutations in the genes coded for the amyloid precursor protein (APP) and proteins known as the presenilins may be involved in APP processing causing inherited AD forms (Bellenguez et al. 2020). Since the 1930s, AD presents an autosomal dominant form of inheritance because rare forms of AD are entirely genetically determined. Until the 1980s, the systematic linkage approaches for characterizing the contributing genes were not developed. In this perspective, three genes, APP, PSEN1, and PSEN2, were responsible for early-onset, dominantly inherited forms of AD coding, respectively, for amyloid precursor protein, presenilin-1, and presenilin-2 (Cacace et al. 2016). The majority of cases of AD are late-onset sporadic forms, with no evident familial aggregation. AD appears to be one of the human multifactorial diseases with the highest heritability level (70%). It has been reported that the e4 allele of the apolipoprotein E (APOE) gene was connected with the risk of early AD (Strittmatter et al. 1993). Since then, with the remarkable exception of some African populations, this group has been detected in approximately all ethnic groups (Farrer et al. 1997; Gureje et al. 2006). Due to the discovery of APOE and the potency of the genetic factor in AD, our knowledge of AD's genetics was expected to amplify speedily. With the discovery of three new genetic risk factors, CLU, CR1, and PICALM in 2009, the publication of the first two large-scale genome-wide association studies (GWASs) of AD formed a landmark field in genetics (Harold et al. 2009; Lambert et al. 2009).

6.3 Treatment Strategies

Based on the pathophysiology and neurochemistry of AD, the treatment strategies are planned accordingly. The pathology of AD is categorized principally by extracellular senile plaques and intracellular neurofibrillary tangles. The pathological hallmark of AD increases protein β-amyloid, also called senile plaques, and neurofibrillary tangles, the collections of tau protein that are hyperphosphorylated as paired helical filaments (Lambert et al. 2009; Athanasios and Stefan 2016). Several hypotheses aimed at explaining the origins of AD and different treatment strategies are discussed below.

6.3.1 β-Amyloid Cascade Hypothesis

Proteolysis of APP leads to the formation of Aβ peptide, an integral transmembrane protein found in different cell types, including neurons and glial cells (Santana et al. 2015; Chiang and Koo 2014). Alternative splicing produces multiple isoforms of the molecule in humans, with APP695 being the most abundant in the brain (Chiang and Koo 2014). Aβ is formed via cleavage of α-, β-, and γ-secretase enzyme protein complexes when APP is processed into smaller peptide fragments which include presenilin and nicastrin molecules (Haass et al. 2012). APP is catabolized by α-secretase and produces soluble sAPPα fragment, which remains in the

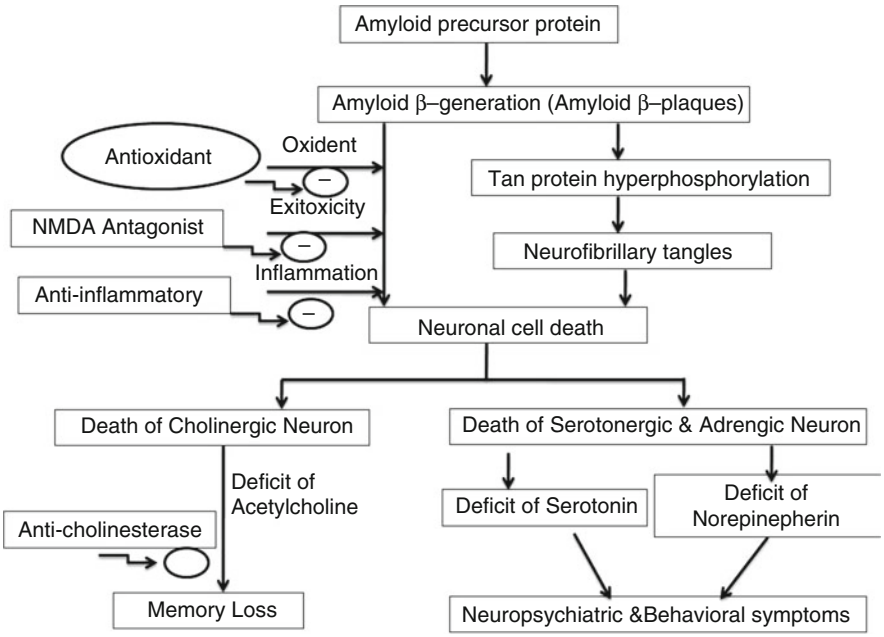

Fig. 6.1 Potential targets for drug action in Alzheimer's disease

extracellular space, and a carboxy-terminal 83-amino acid (C83) fragment, which is anchored in the plasma membrane under physiological conditions (Eriksen et al. 2003; Alvarez et al. 2015). APP is primarily cleaved by β-secretase 1 (BACE), which fragments APP into sAPPβ and a 99-amino acid membrane-bound fraction (C99) in a neuropathological situation. Additionally, processing of the C99 fragment by γ-secretase results in the production of either A(1–40) or Aβ(1–42) peptides, which might lead to the formation of senile plaque (Mucke and Selkoe 2012; Castello and Soriano 2013; Drachman 2014). Aβ peptides may cause synaptic loss, decrease neuronal plasticity, alter energy metabolism, induce oxidative stress and mitochondrial dysfunction, and provoke disruptions in cellular calcium homeostasis, whereas sAPPα is beneficial to humans (Haass et al. 2012; Mucke and Selkoe 2012). The amyloid cascade hypothesis reveals that the development, aggregation, and deposition of Aβ peptides constitute a significant incident in pAD's pathogenesis, which activates neurotoxicity and neurodegeneration (Hardy and Selkoe 2002; Haass et al. 2012) as shown in Fig. 6.1. Increased tau phosphorylation and the formation of neurofibrillary tangles are most probably due to extreme extracellular Aβ. Molecular genetics studies gave acceptance to this hypothesis, signifying the possible novel therapeutics for inhibitors of β- and γ-secretase or enhancers of α-secretase activity. However, in sporadic AD cases, the amyloid cascade hypothesis cannot fully elucidate the root causes of the AD where the generation of Aβ does not show a clear basis of genetics (Nalivaeva et al. 2008).

6.3.2 Strategies Focused on Tau Proteins

Tau proteins have an essential function in stabilizing microtubules, extremely soluble, particularly in axons abundant in the neurons (Cowan and Mudher 2013). Insoluble paired helical filaments (PHF) are formed from hyperphosphorylation of tau, which forms neurofibrillary tangles. Cytoskeleton destabilization was provoked by the loss of microtubule-binding capacity, which ultimately leads to neurons' degeneration and death (West and Bhugra 2015). Tau-centered treatments intend to reduce the phosphorylation and aggregation of Tau protein as a substitute for amyloid-centric strategies. Additionally, microtubule-stabilizing drugs could be used as a disease-modifying approach in AD (Shefet and Benhar 2015). Recently, immunomodulation was recommended as a possible opportunity for promoting adequate clearance of aggregates of TAU proteins.

6.3.3 The Cholinergic Hypothesis

AD is characterized by a progressive loss of learning and memory in addition to neuronal death. The hippocampus is influenced by cholinergic modulation which is the main region of the brain involved in **memory processing** (Konishi et al. 2015). Neurotransmitter alterations are associated with the degeneration of cholinergic neurons in the nucleus basalis of Meynert and the loss of cholinergic inputs to the neocortex and hippocampus. Several studies showed a reduction in choline acetyltransferase (ChAT) and acetylcholine (ACh) release, with decrease in nicotinic and muscarinic receptors in the cerebral cortex and hippocampus of postmortem AD brains (Tata et al. 2014). One of the two classes of drugs approved for treating AD-like acetylcholinesterase inhibitors (AChEI) works by increasing ACh bioavailability at the synapse. But none of these drugs are competent neither in reversing the route of AD nor decreasing the progression of AD (Wallace and Bertrand 2013). Their possible use in combination therapy with other disease-modifying compounds should not be excluded; however, their clinical effect is largely calming. The use of ladostigil (TV3326) improves extrapyramidal symptoms. It provides an antidepressant effect as a reversible inhibitor of AChE and is a selective and irreversible inhibitor of brain monoamine oxidases A and B (Weinreb et al. 2011, 2012). It also appears to be a potent antiapoptotic, antioxidant, anti-inflammatory, and neuroprotective agent.

6.3.4 Dendritic Hypothesis

Dendritic abnormalities come in comparatively early stages of AD. It has just been recently shown that this is where we begin to know the primary molecular changes that occur on the postsynaptic side in the dendrite, although dystrophic neurites, reduced dendritic complexity, and dendritic spine loss are all documented features of AD (Shirazi and Wood 1993; Cochran et al. 2014). Studies documented that soluble

Aβ oligomers are the primary neurotoxic species accountable for the pathology of dendrites. Aβ oligomers might cause anomalous activation of *N*-methyl-D-aspartate receptor (NMDAR) postsynaptically by forming complexes with the cell-surface prion protein (PrPC). PrPC, which interacts with Fyn tyrosine kinase-metabotropic glutamate receptor 5 complex (FynmGluR5), is enriched at the neuronal postsynaptic density. Fyn activation occurs when Aβ is bound to PrPCFyn- mGluR5 complex. Activation of Fyn leads to the tyrosine phosphorylation of the NR2B subunit of NMDAR. This causes initial augmentation and then a loss of NMDARs present at the cell surface (Yang et al. 2011). It has been shown that overexpression of Fyn accelerated the loss of synapse and the beginning of cognitive impairment in the transgenic mouse model of AD; at the same time, its inhibition produced an opposite effect (Cochran et al. 2014). Elevated levels of Fyn in AD brain have been reported in the brain of AD. Moreover, it has been reported that Fyn phosphorylates Tau at Tyr18 residue (Wilkinson et al. 2014). Therefore, Fyn might be a potential target in the treatment of AD.

6.3.5 5-HT$_6$ Receptors in Alzheimer's Disease

Receptors of 5-HT$_6$ are articulated in areas of the CNS implicated in learning and memory. Their inhibition promoted the release of acetylcholine. The restoration of acetylcholine levels is due to 5-HT$_6$ antagonism (Woolley et al. 2001). This hypothesis confirms that 5-HT6 receptor antisense oligonucleotides improve learning and memory in the Morris water maze test in normal rats (Ramirez et al. 2014). Together with AChEIs, 5-HT$_6$ inhibitors might be helpful in amalgamation therapy, such as Lu-AE-58054 (SGS-518) and PF-05212365 (SAM-531), considered as potential treatments for mild-to-moderate AD (De Felice 2013a, b).

6.3.6 Changing the Concept

Clinical studies propose that diabetes is the most important contributing risk factor in AD. There is a close link between insulin-deficient diabetes and cerebral amyloidosis, as demonstrated by research data (Lourenco et al. 2015). Peripheral and central insulin signaling impairments are likely to be present in both diseases. Thus, "type 3 diabetes" theory of AD was developed, which contributes to bridging the experimental metabolic phenotypes present in diabetes and AD into a rational structure (Clarke et al. 2015). Factors such as glucose toxicity, insulin resistance, oxidative stress, elevated levels of advanced glycation end products, and cytokine-mediated neuroinflammation are among the proposed mechanisms by which diabetes could increase the risk of AD development. Recently it has been demonstrated that hypothalamic administration of soluble Aβ oligomers initiates neuroinflammatory cascades which ultimately leads to disorders in peripheral glucose homeostasis (De Felice 2013a, b). Tumor necrosis factor α (TNFα) might play a key role in this process (Lourenco et al. 2013; Risner et al. 2006). As AD and T2DM diseases

are probably linked with each other due to somewhat similar molecular mechanisms, it is rational to presume that drugs used in the treatment of T2DM may have a neuroprotective effect in AD (Gold et al. 2010). It has been studied that thiazolidinediones (TZDs) are an example of antidiabetic compounds having a possible role in AD. Peroxisome proliferator-activated receptor γ (PPAR-γ) has an agonist, e.g., TZDs, which is involved in promoting the PPAR-γ heterodimerization with the retinoid X receptor (RXR) which regulates expression of genes involved in lipid and glucose metabolism. TZDs are known to improve the sensitivity of insulin and decrease cytokine-dependent inflammation (Blalock et al. 2010). Rosiglitazone and pioglitazone are known antidiabetic medicines, which help in regulating glucose homeostasis by increasing insulin sensitivity, reducing blood glucose levels, and improving lipid metabolism. Both medicines have also been studied as potent therapeutics for the treatment of AD. Pioglitazone modified various brain aging indices but did not slow down the cognitive decline studied in animal models (Sato et al. 2011). It has been studied that pioglitazone treatment improved memory and cognition in patients suffering from AD in a clinical trial (Cardoso et al. 2013).

6.4 Future Strategies

AD is a multifaceted pathology that might entail multiple strategies for the treatment. Early disease detection, combination therapies, and lifestyle choices are all likely contributors (Mi et al. 2013; Barnard et al. 2014; Humpel 2011). For the successful eradication of the disease, an extensive range of studies demonstrated insufficient nutrition could augment AD development threat (Cooper 2014). Diet rich in nutrients can progress your probability of not developing AD. However, neither the Mediterranean-type diet nor the antioxidant diet only can prevent AD. Identification of biomarkers indicates primary stages of AD, which can lead to early diagnosis and development extrapolative outcomes. Recently, diagnostic strategies are paying attention to A (1–42) detection and total and phosphorylated Tau levels in the CSF and the brain. Imaging techniques such as brain MRIs are also used (Humpel 2011; Wallon et al. 2012). When the pathology has fully developed for both Aβ and tau increases to use as a diagnostic markers for AD development at primary stages. Another set of molecules which can potentially improve AD pathology is growth factors. Transforming growth factor β family, insulin-derived GFs (insulin-like growth factor 1 (IGF-1) and insulin-like growth factor 2 (IGF-2)), basic fibroblast growth factor (bFGF), and neurotrophins (nerve growth factor, NGF; brain-derived growth factor, BDGF; glial-derived neurotrophic factor, GDNF) all contribute in neurogenesis and neurodevelopment and might be measured as possible targets for AD treatment (Tuszynski et al. 2015; Perry 1986).

6.5 Neurochemistry of AD and Its Association with Treatment

Neurochemical instability is most significant as far as drug treatment of AD is concerned. All the four drugs approved by the Food and Drug Administration (FDA) and their mechanism of action revolve around neurochemical conflicts. There is a cholinergic hypothesis that suggests the deficiency of acetylcholine as the main factor for the symptoms of AD (Paul 2005). However, from the pharmacological approach, the cholinergic hypothesis is most important, but considering the cholinergic deficiency as an exclusive reason for AD symptoms is an overgeneralization. Instead, AD involves many neurotransmitters like glutamate, serotonin, and neuropeptides (Chen et al. 2014).

6.5.1 Drug Treatment of Alzheimer's Disease

Several approaches are in the process of trials based on AD's pathophysiology and neurochemistry, but a cure of AD is vague, and stopping disease progression is still a dispute. None of the drugs has reached the stage of approval although numerous drug trials are ongoing to target amyloid-beta production. Recently permitted drug classes are only for neurochemicals. The two classes are cholinergic modulation and NMDA modulation. The cholinesterase inhibitors and NMDA antagonist at least decelerate the turndown of cognition, behavior, and global AD patients' changes. Though cholinergic and glutamatergic dysfunctions are neurochemical targets for AD's indicative progression, these drugs do not heal the disease (Giacobini 2000).

6.5.2 Cholinesterase Inhibitors

The fundamental idea is to enhance the cholinergic function of the brain. Recently acetylcholinesterase enzyme (AchE) inhibitors are used as a new approach. Acetylcholinesterase is the degrading enzyme of acetylcholine. As per cholinergic hypothesis on AD, there is lack of acetylcholine and inhibition of degrading enzyme. the acetycholine level enhances. The irreversible inhibitors of AchE (e.g., organophosphorus) turn into poisonous ones. Therefore, only reversible high lipid-soluble inhibitors that can cross the blood-brain barrier are used (Yan and Vassar 2014). Anticholinesterase drugs approved by the FDA for AD-related dementia are donepezil, rivastigmine, and galantamine. These drugs have been selected because of their central role in the selection of peripheral ChE inhibition.

6.6 Future Perspectives and New Drug Targets

There is no clear evidence that the current approved drugs help in modifying the primary pathological process of AD. Instead, they only give suggestive relief and slow the process of symptom deterioration. So the search of drugs acting on new

targets is needed, and accordingly, several trials are in the pipeline. Several trials were started, but they didn't get approval, and many of them discontinued due to lack of any considerable advantage in Phase II or III clinical trials. One recent target is β-secretase, namely, β-site APP cleaving enzyme 1 (BACE1). BACE1 cleaves precursor protein. Many compounds are being tried, but none have passed Phase III due to lack of significant efficiency with discontinuation of studies for some compounds (Napryeyenko and Borzenko 2007). Some other targets like tau stabilization, tau aggregation inhibitor, microglial activation inhibitor are new molecules might be passed the clinical trials' phases.

6.7 Alternative or Herbal Medicine for Alzheimer's Disease

Herbal drugs are acquiring enormous fame around the world as far as health is concerned. Lack of allopathic medicines for the treatment of AD has focused interest on herbal drugs. On medicinal herbs, a number of researches have been done. Herbs have pharmacological properties like anti-inflammatory and antioxidant activities that may be used in the treatment of AD. Patients suffering from AD have an acetylcholine deficiency. Anti-inflammatory herbs like chamomile, ginseng, licorice, turmeric, and white willow bark might decrease the brain tissue inflammation in AD. Acetylcholine plays a significant function in cognitive function and reasoning. Brains of the patients suffering from mild-to-moderate AD have unusually low acetylcholine concentrations. This ensures that any compound that augments the cholinergic organization in the brain might help treat AD and related brain failures. For AD, herbs that inhibit acetylcholinesterase (AchE) have natural COX-2 inhibitors, also documented as medicinal herbs. Some other herbs are known for decreasing the degeneration of the brain caused by AD-like Guduchi, Yashtimadhuk, Padma (*Nelumbo nucifera*), Vacha, Convolvulus pluricaulis, Shankhpushpi, Pancha-Tikta-Ghruta Gugguli, Amalaki, Musta Arjun, Amalaki, Ashwagandha, Galo Satva, and Kutaj. They increase the function of the brain and provide constancy when continuously used.

6.7.1 *Ginkgo biloba*

Gingko biloba is used as an extract. Several placebo-controlled trials have been conducted. Numerous of these studies were less well designed and have not been rigorously used in current investigative criteria. A meta-analysis of studies suggested either pathetic or without benefit in patients of AD. Its use as an additional therapy with anticholinesterase has not been estimated in long-term studies (Montgomery et al. 2003).

6.7.2 Acetyl-L-carnitine

Studies utilizing modern diagnostic definitions and conclusion methods have no benefit for ALC. However, meta-analysis of studies with altering definitions, inclusion criteria, and a conclusion has found proof of its use in mild disease. Studies with its add-on to current standard treatments are still going on. No severe side effects have been observed clinically or on an individual (Yang et al. 2005).

6.7.3 Curcumin

No clinical facts of curcumin for AD are available, despite many assert and animal studies, for its function in decreasing oxidative damage and pathology of amyloid protein. However, it is being used for many similar conditions (Lannert and Hoyer 1998). The list of drugs approved by the FDA and future drugs used to treat Alzheimer's disorder is shown in Table 6.1.

6.7.4 *Panax ginseng* (Araliaceae)

Panax ginseng (Ren-shen) possesses saponins, protopanaxadiol, protopantriol, and oleanolic acid saponins known to have memory-increasing properties for the learning destruction persuaded by scopolamine (Park et al. 1996). Ginseng grows in Northeastern Asia. Its roots have been used in folk medicine in countries like China and Korea, for boosting energy from ancient time. For thousands of years, it

Table 6.1 Drug used in Alzheimer's

Drugs	Targets
FDA approved	
Donepezil	
Glantamine	Improve cholinergic deficit
Rivastigmin	
Tacrine	
Memantine	Reduce exitoxicity by glutaminegic action
Future drugs	
Ginkgo biloba	Effects on cerebral blood flow, neurotransmitter systems, direct effect on amyloid aggregation
Acetyl-L-carnitine	Modulate the activity of neurotrophic factors
Lecithin	Accelerate acetylcholine synthesis by increasing availability of the substrate choline
Vinca minor (Vinpocetine)	Improve cerebral metabolism, increase glucose consumption by the brain
Curcumin	Antioxidant and anti-inflammatory properties as well as a direct effect against β-amyloid aggregation

was used as a medicinal herb. The ginseng extract has many uses: it maintains human beings' both physical and mental health (Bilge and Ilkay 2005).

6.7.5 *Glycyrrhiza glabra* (Fabaceae)

Glycyrrhiza glabra is also known as licorice. The effects of a water extract of licorice on Aβ25–35-induced apoptosis in PC12 cells have been investigated. The result suggests that it exhibits a shielding effect against apoptotic death of neurons induced by Aβ fragments. Extract from the licorice root is reported to treat or even prevent brain cell death in diseases like Alzheimer's and its related symptoms (Rubio et al. 2011).

6.7.6 *Commiphora wighitti* (Burseraceae)

A plant resin, *Commiphora wighitti* (Guggulu) constitutes major constituents, guggulipid and guggulsterone. The guggulipid is a possible cognitive stimulator for the progression of memory in scopolamine-induced memory deficiency (Park et al. 1996). Guggulu acts on impairment in learning and memory and reduces choline actyltransferase levels in the hippocampus. However, it shows maximum effects on memory functions and potential for dementia (Kumar et al. 2011).

6.7.7 *Withania somnifera* (Solanaceae)

Active glycowithanolides of *Withania somnifera* (Ashawgandha) have a major antioxidant function, which is attained by increased activities of several enzymes, viz., superoxide dismutase, catalase, and glutathione peroxidise (Sandhu et al. 2010). Ashwagandha is used as a nervine tonic that rejuvenates the cells and boosts energy. The cholinesterase inhibition assessment was carried out using a colorimetric method based on Ellman's reaction and demonstrated that the *W. somnifera* extract significantly inhibited AChE in a concentration-dependent manner (Sandhu et al. 2010).

6.8 Conclusion

This review focuses on the associations between environmental causes and the development of AD and other neurodegenerative disorders. Our information on the genetics of AD has improved extensively over the last few years. But much work remains to be completed to exemplify the missing genetic causes. This must show how to modify treatments that go with the individual patient's genetic report. Present data revealed that AD neuropathology engages numerous signalling cascades. Over the last few years, amyloid protein hypothesis has conquered the

field, due to which many studies have focused on inhibition and elimination of Aβ and senile plaques. Unluckily, the amyloid-centric strategies have failed to exhibit developments in cognition in AD patients. Herbs may take part in the early treatment of Alzheimer's and other disorders like reduced memory and dementia. One of the major benefits is that they have low toxicity compared to modern medicines. As a result, if any person has a family history of AD or has memory problems, they may start taking these herbal medications earlier to delay symptoms or possibly prevent the arrival of the symptoms.

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Therapeutic Potential of Polyphenols in Alzheimer's Therapy: Broad-Spectrum and Minimal Side Effects as Key Aspects

7

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Abstract

Alzheimer's disease (AD) is a degenerative brain disease that is the leading cause of dementia among the human population. AD is characterized by accumulating amyloid plaques which are insoluble deposits of a 4 kDa peptide of ~40–42 amino acids in length, known as amyloid-β (Aβ). The imbalance between Aβ generation and clearance in the brain leads to the progression of AD. AD pathology is characterized by the deposition of oligomeric and fibrillar forms of amyloid-β (Aβ) in the neuropil and cerebral vessel walls. Neurofibrillary tangles are composed mainly of hyperphosphorylated tau and neurodegeneration. Polyphenols are the most abundant antioxidants in the diet. More than 8000 naturally occurring polyphenols exist.

Numerous studies have indicated that high consumption of fruits and vegetables rich in flavonoids and other polyphenols reduces the risk/incidence of age-related neurodegenerative disorders, highlighting the importance of these polyphenols as neuroprotective agents. Due to polyphenols' ability to influence and modulate multiple targets in the cascade of the pathogenesis of neurodegenerative diseases, they are considered a candidate with a promising result against neurodegeneration, halting the progression of the disease. There is now

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substantial evidence indicating that oxidative damage to the brain is an early AD pathogenesis event. Oxidative stress and damage to brain macromolecules are vital processes in neurodegenerative diseases. The antioxidant properties of many polyphenols are purported to provide neuroprotection. There are pieces of evidence that some of the polyphenols can easily cross the blood-brain barrier (BBB). This chapter will provide deeper insights into various polyphenols that play a pivotal role in AD and shed light on the roles of these in the context of AD therapeutics.

Keywords

Alzheimer's disease · Polyphenols · Rosmarinic acid · Resveratrol · Green tea polyphenol · EGCG · Curcumin · Quercetin

7.1 Introduction

Polyphenols are phenolic compounds that constitute one of the most abundantly present secondary metabolites in the plant kingdom. Plant polyphenols were earlier referred to in the literature as vegetable tannins due to the tanning effect on animal skin (Bate-Smith et al. 1962). Structurally, the compounds are characterized by one or more hydroxyl groups attached to the aromatic ring (Tsao 2010). Polyphenols constitute a well-differentiated group in terms of the chemical structure and biological activities as well. Their occurrence is conjugated chiefly with sugars, amines, lipids, acids, and other phenols. The classification in different groups is based on the number of phenol rings and structural elements attached to the rings (Pandey and Rizvi 2009; Pimpão 2014). The primary classes are phenolic acids, flavonoids, stilbenes, coumarins, and lignans (Fig. 7.1).

Phenolic acids are represented by hydroxybenzoic and hydroxycinnamic acid. Hydroxybenzoic is rare in its contribution to the human diet, with a few exceptions: gallic acid and ellagic acid (Manach et al. 2004). Hydroxycinnamic acid, on the other side is common with candidates such as caffeic acid, ferulic acid, sinapic acid, shikimic, and tartaric acid (Pandey and Rizvi 2009). The second group, flavonoid,

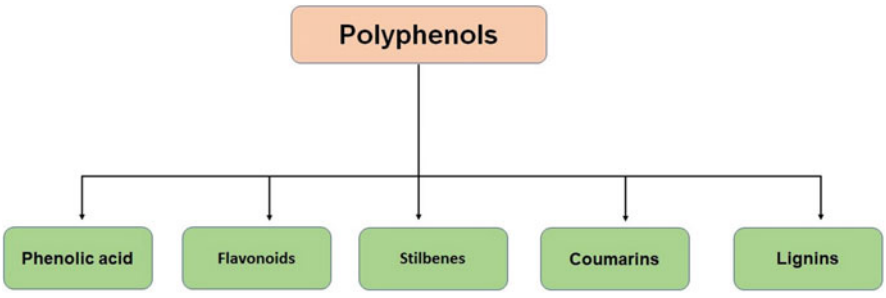

Fig. 7.1 Classification of polyphenols

is the most studied group. More than 10,000 different structures have been incorporated in this group with a common basic structure consisting of two aromatic rings bound together by three carbon atoms that form an oxygenated heterocycle (Cheynier et al. 2013). This phenol class is responsible for mesmerizing and alluring colors presented by fruits, flowers, and leaves.

The most diverse group is subdivided into six subgroups: flavonols, flavones, isoflavones, flavanones, anthocyanins, and flavanols. Differences within each group arise due to the functional hydroxyl arrangement, its number, and alkylation and glycosylation capabilities (Spencer et al. 2008). Some of the commonly known flavonoids are quercetin, myricetin, kaempferol, etc. Stilbenes are not so common in diet except for resveratrol found in grapes and red wine. The group is structurally characterized by a two-carbon methylene bridge connecting two phenyl moieties (Cassidy et al. 2000). The fourth group, coumarin, is made of an aromatic ring linked to a condensed lactone ring. The fifth group is lignans, which are diphenolic compounds formed by dimerization of two cinnamic acid residues. The richest dietary source is linseed, containing secoisolariciresinol and low quantities of matairesinol (Adlercreutz and Mazur 1997)

Fruits and vegetables are mainly considered to be the richest source of dietary polyphenols. Hence, a healthy diet contains a cocktail of several phenolic compounds in varied chemical forms (Lewandowska et al. 2016). It's a challenging task to determine the daily intake of polyphenols due to every person's variable dietary pattern. On average, it is estimated that a normal person takes about 14 mg of flavonoids per day (Scalbert and Williamson 2000). Polyphenols are one of the largest sources of antioxidants in the diet. However, the total phenolic content does not directly correspond to the total antioxidant activity (Pérez-Jiménez et al. 2010). The metabolism and absorption of phenolic compounds are essential for their bioavailability, which is responsible for their significant biological activity. However, absorption and metabolism are affected by the polyphenol's chemical structure and factors related to interpersonal variabilities, such as systemic factors like age, gender and pathologies, and the level of enzymatic activities.

Considering the largest class of polyphenols, the cleavage of the flavonoids can occur in the stomach with a very low pH. Flavonoids are degraded into smaller phenolic acids by the colon's microflora, enabling them to be absorbed into the cells and even cross the BBB (Spencer et al. 2004). The crossing of the BBB by polyphenols is well evident; studies in situ, in vitro, and in silico showed polyphenol structure, and efflux systems influence their brain bioavailability (Youdim et al. 2004; Figueira et al. 2017). However, the exact mechanism and route by which they cross the barrier is still unclear. Most of the metabolites are lost in the urine and contribute to a lower bioavailability (Spencer et al. 2004). Despite having phenotypical differences, neurodegenerative diseases have few common factors, such as oxidative stress and inflammation. Our bodies have an endogenous mechanism to maintain redox homeostasis to deal with overproduced free radicals in oxidative stress. Somehow, these mechanisms seem to be inefficient in pathologic contexts, making exogenous sources of antioxidants capable of dealing with oxidative stress so crucial. Among these, dietary polyphenols have been extensively studied for their

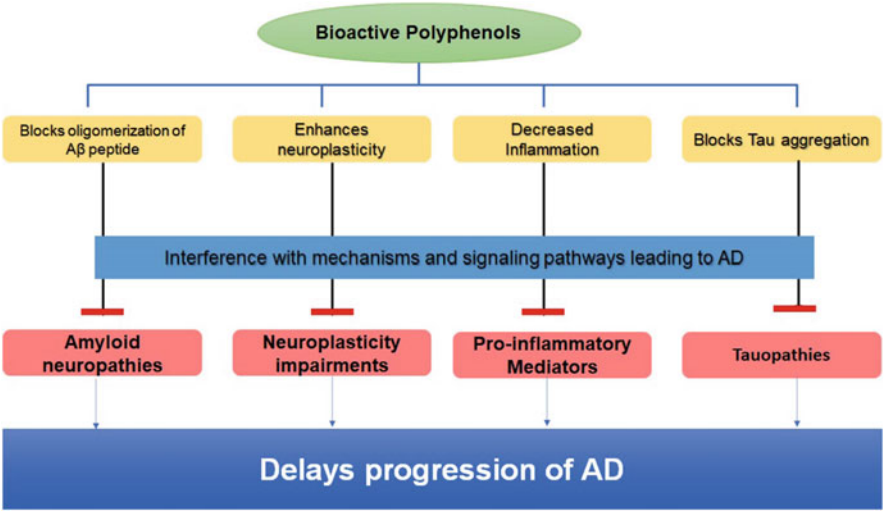

Fig. 7.2 Flowchart depicting different bio-effects of polyphenols

strong antioxidant capabilities. Among the possible known mechanisms, the scavenging of free radicals by binding with polyphenols postulated under the radical elimination hypothesis shows deleterious effects on free radicals (Das et al. 2016). However, strategies for the antioxidant activity go beyond the neutralization of free radicals having a modulating effect on the signaling pathways (Han et al. 2007).

Figure 7.2. shows a flowchart that depicts different bioeffects of polyphenols. The well-fortified effect of polyphenols is majorly due to their capability to regulatory effects on signaling pathways related to diseases, such as PGC-1α (Pasinetti et al. 2015), SIRT1 (Wu et al. 2017), AMPK (Jiménez-Flores et al. 2014), MAPK which further regulates extracellular signal-regulated kinases (ERK), the p38 MAPKs, and the c-Jun NH2-terminal kinases, NF-*k*B, activator protein 1, canonical Wnt, and protein kinase C (PKC) (Das et al. 2016; Kaulmann and Bohn 2016). These pathways play a crucial role in many biological functions, such as apoptosis, cell proliferation, and many more (Das et al. 2016; Kaulmann and Bohn 2016). The role of polyphenols as signal regulators is due to redox-sensitive changes on the cascades. These phenolic compounds are engaged in several pathologies and are used as a drug to hit many targets involved in neurodegenerative diseases, cancer, and other pathologies (Upadhyay and Dixit 2015).

7.2 Polyphenols for Prevention and Treatment of Various Diseases

Table 7.1. provides an insight into the mechanism of different polyphenols specifying their bioactivity.

Table 7.1 Mechanism of different polyphenols specifying their bioactivity

Bioactivity	Polyphenols/compounds	Mechanism	References
1. Antioxidant	(i) Green tea polyphenols	(a) Increase in total capacity of serum and blood plasma	Kumar and Pandey (2013)
	(ii) Quercetin, rutin, EC	(a) Metal chelator (b) ROS scavenging (c) Increases the production of endogenous enzymes	da Silva Pinto (2013), Kukula-Koch et al. (2013), Kumar and Pandey (2013), Mishra et al. (2013), Bruno et al. (2014)
	(iii) Theoflavins and thearubigins	(a) Increase in the antioxidant parameters of blood (b) Significant reduction in lipid profile, glucose content, and renal function (c) Increases insulin levels	Arent et al. (2010), Imran et al. (2018)
2. Anticancer	(i) Quercetin	(a) Lung cancer inhibition by the antiproliferative effect on HepG2 and A549 cell lines	Dahiya et al. (2019a, b), Gupta et al. (2019a, b)
		(b) Inhibition of tumor progression and invasion (c) Angiogenesis inhibition	Hashemzaei et al. (2017), Song et al. (2017)
		(d) Inhibition of kinases involved in cancer progression	Khan et al. (2017)
	(ii) Rutin and vanillin	(a) Inhibition of cell viability of MCF-7 and HeLa cells in a dose-dependent manner (b) Inhibition of MAP-kinases involved in cancer progression (c) Apoptosis induction	Dahiya et al. (2019a, b), Gupta et al. (2019a, b)
	(iii) Ellagic acid	(a) Lung cancer inhibition by the antiproliferative effect on HepG2 and A549 cell lines (b) Inhibition of kinases like PDK3 and SPHK1 involved in major signaling pathways leading to cancer	Lee et al. (2010), Zhao et al. (2017)
	(iv) Hesperidin	(a) Apoptosis induction (b) Increasing cleaved caspase-3 protein expression levels	

(continued)

Table 7.1 (continued)

Bioactivity	Polyphenols/compounds	Mechanism	References
3. Anti-inflammatory	(i) ECGC	(a) Decreases pro-inflammatory chemokine production (b) Inhibits proliferation of autoreactive T cells (c) Reduces the production of autoimmune agents	Pae and Wu (2013), Wu (2016)
	(ii) Rutin, quercetin, virtexin	(a) Significantly reduces NO, MPO, and TNF-α (inflammatory mediators) production	Nikfarjam et al. (2017)
	(iii) Apigenin	(a) Inhibits the production of pro-inflammatory cytokines, Th1 cytokines, TNF-α, interferon-gamma (IFN-γ), and interleukin-2 (IL-2)	Zhang et al. (2016)
4. Cardiovascular disease prevention	(i) Green tea polyphenols	(a) Reduces both systolic and diastolic blood pressures (b) Significant reduction of C-reactive protein levels, TNF-α, insulin levels, insulin resistance, and fasting serum glucose	Bogdanski et al. (2012)
	(ii) EGCG	(a) Significant decrease in blood pressure (b) Increased nitric oxide production from endothelium through a PI-3-kinase pathway	Potenza et al. (2007)
5. Antidiabetic activity	(i) Naringin	(a) Inhibits inflammation and insulin resistance by stopping the activation of the MAPK pathways and alternatively by activating IRS-1 (b) Lipid reduction by inhibition of synthesis and increased fatty acid oxidation (c) Hypoglycemic effect by regulating PEPCK and G6pase activity in the liver	Pu et al. (2012)
	(ii) Hesperidin	(a) Reduces blood glucose level by decreased activity of G6Pase and an increase in the expression of GK (b) Decreases in glucose export through glucose transporter membrane proteins	Akiyama et al. (2009)
	(iii) Quercetin	(a) Significant glucose uptake through the insulin-independent AMPK pathway (b) Inhibition of mitochondrial ADP-stimulated oxygen consumption (c) Inhibition of ATP synthase in mitochondria	Eid et al. (2010)

	(iv) Rutin	(a) Decreases in the concentration of plasma glucose (b) Increase in blood insulin level (c) Restoration of glycogen content (d) Protective effect toward pancreatic cells (reduced fatty infiltrate of the Langerhans islets)	Prince and Kamalakkannan (2006)
	(v) Catechins	(a) Inhibitory effect on intestinal glucose uptake (b) Effective in the reduction of glucose uptake under both sodium-dependent and sodium-free conditions	Johnston et al. (2005)
6. Neuroprotective and anti-AD activity	(i) Several dietary polyphenols (e.g., tea catechins, apigenin, quercetin, rutin, vanillin)	(a) Dietary polyphenols are a major class of compounds active toward the inhibition of α-synuclein (b) Significant reduction in the hazard ratio for probable Alzheimer's disease (c) Anti-tau effects (d) Inhibition of SH-SY5Y cell line	Masuda et al. (2006), Khan et al. (2017)
	(ii) EGCG	(a) EGCG directly converted fibrillar species into benign protein aggregates (b) Inhibition of α-synuclein and amyloid-β-fibril formation by EGCG through direct binding to β-sheet-rich aggregates (c) Activation of PKCα and PKCε which leads to increased production of neuroprotective, non-amyloidogenic sAPPα (d) Inhibition of SH-SY5Y cell line	Levites et al. (2003), Bieschke et al. (2010)
	(iii) Wine-derived polyphenols (morin, myricetin, quercetin, catechin, kaempferol, epicatechin)	(a) Anti-AD effects (b) Inhibition of β-amyloid formation in a dose-dependent manner (c) Destabilization of preformed β-amyloid aggregation	Ono et al. (2003)

7.3 Neurodegeneration and Role of Polyphenols

Neurodegenerative disorders (NDs) are diseases that collectively lead to debilitating and fatal conditions affecting neurons. These neurological syndromes are chronic and cause dysfunction of the nervous system due to neuronal cell failure (Brettschneider et al. 2015), ultimately leading to dementia and ataxia. Hereditary and/or sporadic conditions lead to the progression of the syndromes, which exerts a deleterious impact on the central nervous system (CNS) and the peripheral nervous system (PNS) (Soto 2003). Therapies to entirely modify the diseases by delaying or reversing disease progression are not available. Hundreds of disorders afflict the nervous system, such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), degenerative nerve diseases, brain cancer, encephalitis, stroke, prion diseases, etc. NDs are heterogeneous and have multiple factors responsible for the pathology, affecting brain structure. AD, HD, PD, and ALS share misfolded protein aggregation as common pathology, designated as protein conformational disorders (Quist et al. 2005). AD, a clinical syndrome, is characterized by degeneration of neocortical neurons and the hippocampus part of the brain (Braak et al. 1996), responsible for major symptoms like loss of memory and cognitive decline (O'Brien and Wong 2011). PD, the most common motor neuron disease, has clinical symptoms such as bradykinesia, muscle rigidity, resting tremor, and postural instability caused by the loss of dopaminergic neurons in the substantia nigra pars compacta (Lees 2007). Lewy bodies (LBs), the cytoplasmic inclusions, enclose aggregated α-synuclein which is the disease's hallmark (Shults 2006). HD displays many symptoms including dementia, chorea, and emotional disturbance (Martin and Gusella 1986; Walker 2007). The striatal region of the basal ganglia suffers a neuronal demise. HD is linked to genetic mutation linked to the expression of N-terminal polyglutamine (polyQ)-Huntingtin (Htt) beyond a length of ~35 glutamine residues. Cleavage of these polyQ tails produces cytotoxic fragments with a high tendency to cross-link and aggregate in neurons and glial cells (Tydlacka et al. 2008; Bugg et al. 2012). ALS is a fatal disease of motor neurons that can cause death within a few years of the condition's onset. The primary reason for death is respiratory failure. The disease is caused by progressive loss of bulbar, cortical, and ventral cord motor neurons, with the major genetic risk factors being mutations in the genes encoding the superoxide dismutase SOD1 (Rosen et al. 1993), the TAR-DNA-binding protein (Sreedharan et al. 2008), and the fused in sarcoma or translocated in liposarcoma protein (FUS/TLS) (Kwiatkowski et al. 2009; Vance et al. 2009). Neurodegeneration is known to have multiple underlying factors, and polyphenols present pleiotropic effects (antioxidant, anti-inflammatory, antitumor, anti-tau, immunomodulatory properties, etc.; Kimura et al. 2010). Polyphenols have been implicated as potential protective, curative, and preventive agents for many diseases, such as AD (Silveira et al. 2019), Parkinson's disease (Aquilano et al. 2008), Huntington's disease (Maher et al. 2011), hypercholesterolemia (Zou et al. 2003), diabetes mellitus (Bahadoran et al. 2013), chronic fatigue syndrome (Gupta et al. 2009), stroke (Wang et al. 2013), many cancers (Zhou et al. 2016), autism (Parker-

Athill et al. 2009), cardiovascular disease (Perez-Vizcaino et al. 2006), and vitiligo (Jalel et al. 2009), among others (Das et al. 2016). Due to polyphenols' ability to influence and modulate multiple targets in the cascade of pathogenesis, they are considered a candidate with a promising result against neurodegeneration, halting the progression of the disease. For many years, polyphenols were thought to protect cell constituents against oxidative damage through direct scavenging of free radicals. Such an idea has become very popular, leading to several studies exploring this property of polyphenols for NDs since oxidative stress constitutes an important hallmark of these diseases.

The emerging acceptance of polyphenols and their derivatives shows an effect on inhibition of specific protein kinases and lipid kinase signaling pathways (Williams et al. 2004). Several other neuroprotective functions of polyphenols are contributed due to properties like iron chelators (Griffioen et al. 2006), interference with signaling pathways associated with neurogenerative diseases (Spencer 2010), inhibition of neuropathological processes (Rezai-Zadeh et al. 2005), and regulation of mitochondrial function (Surh et al. 2001; Mandel and Youdim 2004; Skupień et al. 2006).

7.4 Role of Some Important Polyphenols in AD

Aging alters an individual's normal functioning as time passes by (Queen and Tollefsbol 2010); it deteriorates and weakens the overall biological system. The primary effect is faced by the brain and cognitive functions, affecting memory, calculation, thinking, learning, and judgment. The effects are so severe that it changes the overall physiology and behavior; AD is a severe problem with millions of new cases every year (World Health Organization 2018).

Tau protein and the amyloid-β peptide (Aβ) are thought to be the key regulators in AD. Both the proteins self-assemble to form amyloid plaques and neurofibrillary tangles, respectively, which are well-known hallmarks of AD. Amyloid plaques with 40/42 ($A\beta_{40}$ and $A\beta_{42}$) amino acids are extracellular accumulations formed as a by-product of APP metabolism. Mutations in the gene PSEN1 and PSEN2 of the APP leads to overproduction of $A\beta_{42}$. The imbalance between production and clearance of Aβ is assumed to the major process of pathology. Oligomerization of Aβ has been reported to be the prime cause of neuronal death and synaptic dysfunction. The tau hypothesis of AD progression claims that the accumulation of tau proteins tangled together leads to the progression of this condition. Tangle formation disintegrates the microtubule assembly and structure of the neuronal cells. The communication between neurons is interfered with, leading to brain cell death. Naturally occurring polyphenols have shown deleterious effects on these hallmarks by targeting the associated signaling pathways (Zheng et al. 2019). Polyphenols alter the amyloid-β precursor protein's enzymatic processing and block toxic Aβ oligomerization by upregulating the clearance of $A\beta_{42}$ monomer, modulating monomer interactions, and remodeling oligomers nontoxic forms.

Additionally, polyphenols prevent tau hyperphosphorylation and inhibit the formation of tau β-sheet. The anti-Aβ-self-assembly and anti-tau-self-assembly effects of polyphenols increase their potential as preventive or therapeutic agents against AD, a complex disease with many pathological mechanisms. Polyphenols are excellent antioxidants, and several in vivo experiments have been conducted to find an association between polyphenol-rich food and amyloid accumulation (Hu et al. 2013). AD risk was reduced to half in a group of mice fed with food and rich in polyphenols and pomegranate, a good source of polyphenols (Hartman et al. 2006). Resveratrol from grape extracts reduced hippocampal neurodegeneration in transgenic mice (Kim et al. 2007).

The pathophysiology has a direct relation to oxidative stress related to neurons. Oxidative stress causes neuronal damage and disrupts the intracellular signaling leading to apoptosis (Ramassamy 2006). With continued aging, the central nervous system becomes more susceptible and affected by oxidative stress (Joseph et al. 2005). In the early stages, the Aβ amyloid peptide exploits many mechanisms to damage neurons, including mitochondrial dysfunction, apoptosis, and NF-kB activation. Plaque toxicity involves forming reactive oxygen species (ROS) and metal transitions (Kaltschmidt et al. 1997, 1999; Longpré et al. 2006). Antioxidants from the diet have a strong negative correlation with the factors promoting AD. Several experimental evidence of dietary and naturally occurring polyphenols in curbing the menace of AD are present. Flavonoid derivatives have been tested in vitro on rat acetylcholinesterase (AChE) and shown better inhibitory activity than the marketed drug rivastigmine, while a few demonstrated inhibitory activities similar to donepezil (Kumar et al. 2016). Flavanols, catechins, and epicatechins in research proved to be very promising against AD. However, many others have also reversed the impact of AD, some of which are extensively approached in the following sections.

7.4.1 Rosmarinic Acid

Rosmarinic acid is a naturally occurring phenolic compound, an ester of caffeic acid and 3,4-dihydroxyphenyl lactic acid, generally found in plants of Lamiaceae (the mint) family that possess broad-spectrum therapeutic potential (Shamsi et al. 2020a, b). RA has been well studied for different biological activities ranging from anticancer to neuroprotective activities (Anwar et al. 2020; Shamsi et al. 2020a, b). RA is known to suppress various cancer types (Anwar et al. 2020) by interfering with the signaling pathways involved in the upregulation of metastasis like ERK. RA targets a major factor in the MAP kinases cascade. In vitro and in vivo studies have given evidence for the potency of RA in AD therapy. Computation technique like docking simulation has helped investigate binding efficiencies and affinity of RA to Aβ peptide (Ramazzotti et al. 2016). Many mechanisms contribute to the anti-AD effect of RA; one such is a reduction in amyloid-β (Aβ) secretion by increasing the synthesis of monoamines. Amyloidosis, the formation of amyloid aggregates, is the hallmark of systemic and neurodegenerative disorders. In RA's

presence, there is increased production of monoamine synthesis like epinephrine, 3,4-dihydroxyphenylacetic acid, and levodopa with the enhancement of dopamine signaling pathways. The monoamines are responsible for the degradation of amyloid-β production (Hase et al. 2019). Oligomerization and aggregation of Aβ are inhibited in the presence of RA (Ono et al. 2012), which inhibits AD progression. PC12 cells were cultured and treated with Aβ1–42. Cell cytotoxicity was observed with ROS formation, DNA fragmentation, lipid peroxidation, caspase-3 activation, and hyperphosphorylation tau; all the effects were suppressed in 10μM RA (Iuvone et al. 2006). RA's potential AD effect was studied in vivo by administrating RA orally to mice for 14 days in AD mice. The outcomes were favorable with restored memory and neuromotor functions (Lee et al. 2016). Tau hyperphosphorylation and aggregation are known to promote AD. RA has been studied for its effects on tau as a potential candidate against AD. RA binds to tau in a manner that inhibits β-sheet assembly, demonstrating the effect of RA as an anti-AD polyphenol (Shan et al. 2016; Cornejo et al. 2017).

7.4.2 Resveratrol

Resveratrol, a naturally occurring polyphenol, chemically known as trans-3,4′,5-trihydroxystilbene, is known to exert beneficial effects against AD (Baur et al. 2006; Lagouge et al. 2006) by influencing cognitive impairments (Lagouge et al. 2006; Ranney and Petro 2009). The compound is a known modulator of a few important metabolic proteins such as peroxisome proliferator-activated receptor γ co-activator-1α (PGC-1α), sirtuin 1 (SIRT1), and AMP-activated protein kinase (AMPK) which are involved in the progression of AD and other neurological disorders (Um et al. 2010; Vinciguerra et al. 2010; Vingtdeux et al. 2011). Resveratrol has been shown to benefit in vitro models of epilepsy, AD, HD, PD, ALS, and nerve injury (Rocha-González et al. 2008). The polyphenol belonging to the stilbene subclass is not very abundant in nature; a low concentration of the compound is found in some food sources such as red grapes and its by-products such as juice and wine, some berries, etc. (Sanders et al. 2000; Rimando et al. 2004). A study demonstrated that subjects with mild cognitive impairment showed significant memory function improvement after consuming purple grape juice (Krikorian et al. 2010). Similarly, in another study, it was found that moderate red wine consumption proved beneficial in AD-type cognitive deterioration in the Tg2576 transgenic mouse model of AD by exerting a negative effect on Aβ neuropathology (Ho et al. 2009). This AD model showed a steep decrease in the generation of Aβ peptide in the hippocampal neuron cultures generated from these mice (Vingtdeux et al. 2008). Many ongoing research pieces have claimed control on Aβ accumulation by resveratrol facilitating the proteolytic clearance in neurons (Vingtdeux et al. 2010). Resveratrol shows anti-amyloidogenic effects by exerting modulating effects on AMPK (Vingtdeux et al. 2010).

7.4.3 Green Tea Polyphenol: EGCG

Asian countries traditionally consume green tea extracted from the *Camellia sinensis* plant (Khokhar and Magnusdottir 2002). Green tea is rich in polyphenols with four major derivatives based on structural variance which are epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin-3-gallate (EGCG), with EGCG being the major one (Nanjo et al. 1996; Khan et al. 2006). In the past few decades, green tea has gained a lot of attention mainly due to its active compound EGCG, which is a known therapeutic agent targeting neurodegeneration (Weinreb et al. 2004; Guo et al. 2005), inflammation (Singh et al. 2010), and cancer. EGCG is a well-known radical scavenger (Weinreb et al. 2004), anti-inflammatory agent (Singh et al. 2010), antioxidant (Weinreb et al. 2004), and metal chelator (Lambert and Elias 2010), which makes it a suitable drug candidate against neurodegenerative diseases and other disorders. The metabolism of green tea polyphenols has also been studied, and it was reported that these polyphenols are absorbed, metabolized, and excreted within 24 h from the body. With a few cups of green tea ingestion in a day, the concentrations of polyphenols in plasma increased by more than ten times, sufficient to exert antioxidant activity against all the oxidative damages (Lee et al. 1995; Sharma et al. 2007). EGCG's radical scavenging properties have been measured compared to vitamins E and C, and polyphenol overtook them (Nanjo et al. 1996). Within the derivatives, the order of protective effects in vitro has been reported to be ECG > EGCG > EC > EGC (Nie et al. 2002) and their order of antioxidant potential, EGCG ≥ ECG > EGC > EC (Weinreb et al. 2004).

The extensive researches on EGCG have uncovered its potential to promote aging by exerting functional and morphological alterations on the human brain, like suppression of cognitive dysfunction (Unno et al. 2004), enhancement in the learning process (Unno et al. 2007), and reduction in oxidative damage to the brain (Unno et al. 2007; Schaffer et al. 2012). In AD, EGCG has shown ROS inhibition, degradation of Aβ, and γ-secretase activity, hence clearing off amyloid accumulations. Increased α-secretase activity and suppression of tau have also been observed (Lim et al. 2013). Advances in the mechanism by which EGCG acts on AD and other related conditions have been well studied. EGCG modulates many essential signaling pathways such as MAPK, PKC, PKA, and PI3K/AKT pathways (Mandel et al. 2005; Kalfon et al. 2007). Tau protein and amyloid-β are the two biomarkers of AD, and their inhibition leads to the prevention of AD (Singh et al. 2015). In vitro studies on neuronal cells treated with 10μM EGCG show neuroprotective effects by inhibiting Aβ-induced cytotoxicity; EGCG also acted as an excellent acetylcholinesterase inhibitor (Okello et al. 2012; Qin et al. 2012). The ability of ECGC as a ROS scavenger confers neuroprotective effects against A-β-induced neuronal apoptosis (Choi et al. 2001). EGCG acts as a metal chelator by inhibiting Al (III)-induced fibrillation of toxic amyloid-β and further converting Aβ42 monomers into a folded conformation. Tau aggregation and oligomerization are also inhibited, and at the exact time, the reversal of oligomers to unfolded monomeric state occurs (Wobst et al. 2015). Administration of ECGC in AD

transgenic mice suppressed phosphorylation of tau isoforms and regulated the tau profile (Rezai-Zadeh et al. 2008). Long-term administration of the polyphenol in rats significantly improved spatial cognitive learning abilities (Haque et al. 2006). All the literature and experiments showed ECGC's ability to reduce tau toxicity and Aβ fibrillation and toxicity, thus showing its ability to prevent AD.

7.4.4 Curcumin

Curcumin is the active component of *Curcuma longa*, a widely grown spice in India and other Asian and Middle East companies. It has been used extensively in the Ayurvedic medical system as a pain reliever, antiseptic, and anti-inflammatory agent; the compound is also known to have anticancer properties (Shishodia et al. 2005; Kunnumakkara et al. 2017). Effects of curcumin on AD and its reversal have been studied extensively; in research on the prevalence of AD in India, a lower risk factor of the disease in the population was found (Ganguli et al. 2000; Ng et al. 2006). Inflammation of the nerve cell is one of the pathogenesis in AD (Mishra and Palanivelu 2008). Associated inflammatory changes are the presence of pro-inflammatory factors that accompany the deposition of amyloid-β peptide. Patients with prolonged use of nonsteroidal anti-inflammatory drugs (NSAID) showed a reduced risk of developing AD. However, prolonged use can lead to toxic effects on the human body (Mazzolani and Togni 2013). Curcumin, a potent anti-inflammatory agent, has shown a reversal in AD by various mechanisms. Curcumin is found to inhibit phospholipases, cyclooxygenase (COX-2), enzymes, and transcription factor involved in metabolizing the membrane phospholipids into prostaglandins (Shen and Ji 2012). ROS reduction, inhibition of factors such as NF-κB and AP-1, which are involved in the expression of amyloid and linked to AD by inhibiting pro-inflammatory cytokines activation like Tumor necrosis factor α (TNFα) and interleukin β (IL-β), IL-1 and IL-6 (Park and Kim 2002; Kim et al. 2005). Curcumin is also a proven antioxidant and acts as a neuroprotectant against AD and other ND diseases (Hewlings and Kalman 2017). Aβ levels in AD mice were reduced to 40% with low doses of curcumin compared to control. A 43% decrease in plaque formation was also observed. Low doses of curcumin over a more extended period proved beneficial; however, higher doses surprisingly showed less effect. The compound binds to Aβ at higher concentrations and blocks its self-assembly (Yang et al. 2005). Curcumin easily crosses the blood-brain barrier and binds to the plaques; majorly, Aβ40 aggregation is targeted for inhibition by curcumin (Narlawar et al. 2008). Various other studies also demonstrated the same results, showing the compound's deleterious effect on senile plaques (Garcia-Alloza et al. 2007). Curcumin also promotes phagocytosis of Aβ, clearing the depositions from the AD brain (Fiala et al. 2007). Metal toxicity-induced Aβ aggregation was also reversed; curcumin interacts with heavy metals such as cadmium and prevents neurotoxicity from contributing to AD and related conditions (Baum and Ng 2004; Daniel et al. 2004).

7.4.5 Quercetin

Quercetin (3,5,7,3′,4′-pentahydroxyflavone) (QC), a polyphenol under subgroup flavonoid, is generally found in fruits and vegetables. Many studies have reported diverse quercetin activities, namely, anti-inflammatory, antithrombotic, anti-obesity, anti-hypercholesterolemic, anti-atherosclerotic, and anticancer (Wang et al. 2014; Dahiya et al. 2019a, b; Gupta et al. 2019a, b). The neuroprotective effects of quercetin have been studied extensively, and the results are promising. At low concentrations, QC neutralizes cell toxicity caused by oxidative stress in neuronal cells. QC challenges the hallmarks of AD. It interferes with the formation of neurotoxic Aβ species, prevents its oligomerization, and destabilizes the fibrils (Regitz and Wenzel 2014; Caruana et al. 2016). QC inhibits β-secretase1 enzyme activity by binding to it with hydrogen bonds; the hydroxyl group at C3 has a significant role in inhibiting the enzyme that promotes AD (Shimmyo et al. 2008). It stimulates the regeneration of neurons by downregulation of pro-inflammatory cytokines, such as NF-kB and iNOS (Regitz and Wenzel 2014; Jantan et al. 2015; Costa et al. 2016). NF-κB plays a significant role in assisting APP cleavage and amyloid-β formation. QC-induced NF-κB inhibition was investigated, which showed inhibition of the cytokine (Shimmyo et al. 2008; Paris et al. 2011). Tauopathies commonly lay their roots in the brain's hippocampal region, hampering the cognitive abilities related to the region and further expanding to other regions of the brain. QC decreased tau phosphorylation and the formation of NFTs (Sabogal-Guáqueta et al. 2015). Kinases and phosphatases play a regulatory role in tau hyperphosphorylation. Protein phosphatases keep a check on kinase activity, and the imbalance between the two can cause AD progression. Quercetin reverses tau proteins' hyperphosphorylation via PI3K/Akt/GSK3β and MAPKs signaling pathways (Jiang et al. 2016). Acetylcholinesterase (AChE) is an enzyme responsible for the degradation of acetylcholine (ACh), leading to cognitive symptoms of AD. Inhibiting AChE is a common method to treat mild and moderate types of AD (Abdalla et al. 2014). QC inhibits AChE, balancing the levels of Ach in synaptic cleft thus reversing the progression of the disease (Abdalla et al. 2013).

ROS is formed in the cells by oxidative damage, a major contributor to various neurodegenerative disorders (Kennedy et al. 2016). Aβ is known to exert oxidative damage on neurons (Kennedy et al. 2016). QC, a potent antioxidant, has been shown to efficiently reduce superoxide free radicals (Alok et al. 2014). QC is a radical scavenger, and it modulates the cell's antioxidant properties by activating antioxidant enzymes such as paraoxonase-2 (PON2). Nrf-2 is a regulator of the cell's defense against oxidative stress. The pathway linked, the Nrf-2-ARE pathway, has several enzymes downstream that play a significant role in forming and destroying misfolded and aggregated proteins in AD (Lakhanpal and Rai 2007; Kaur et al. 2013). Figure 7.3. depicts a diagrammatic representation of the involvement of polyphenols with different signaling pathways that are implicated in neurodegenerative disorders.

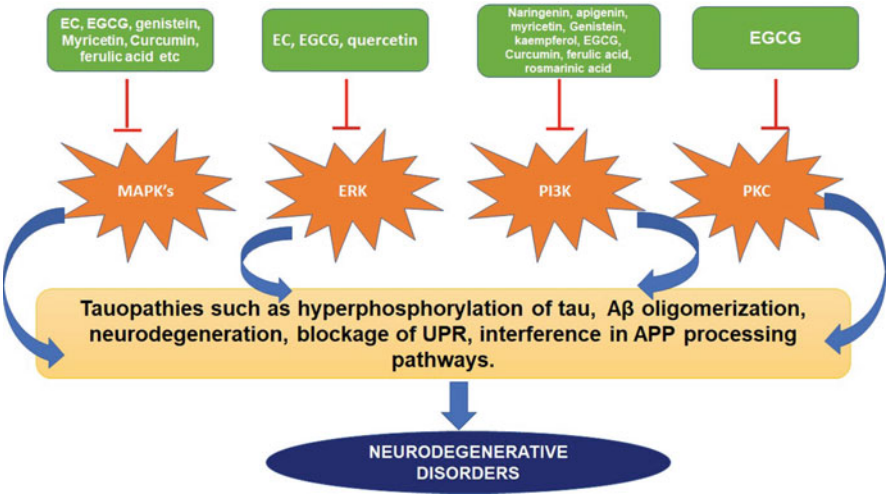

Fig. 7.3 Diagrammatic representation of involvement of polyphenols with different signaling pathways that are implicated in neurodegenerative disorders

7.5 Conclusion

With no cure and several unclear underlying mechanisms, the search for new drug candidates is never lasting. Modern research focuses on various alterable factors such as diet, which can play a significant role in the progression and suppression of AD. Nutrients are primarily researched to find the missing links between neurodegeneration and its reversal. Many nutrients present in our diet have altering effects on the biochemical pathways and energy sources, thereby encouraging us to study CNS and neurodegeneration. This chapter delineates the importance of different polyphenols in the prevention of AD. These act as protective agents by different mechanisms, and this has been discussed in detail, highlighting the beneficial importance of consuming these in our diet. Oxidative stress and damage to brain macromolecules are essential processes in neurodegenerative diseases. In lieu of the fact that polyphenols are excellent antioxidants and several in vivo experiments that have been conducted to find an association between polyphenol-rich food and amyloid accumulation, these are known to have therapeutic potential to treat AD. Moreover, recent studies have shown that polyphenols have an inhibitory effect on kinases such as MARK4, a key player in tau phosphorylation leading to AD pathology. The inhibitory effect of different polyphenols has been studied for other kinases as well, viz., SPHK1 and PDK3, which is implicated in AD pathology highlighting the imprtance of polyphenols in AD prevention by targeting inhbition of the kinases.

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Conflict of Interest The authors declare no conflict of interest.

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Recent Advances in Alzheimer's Disease in Relation to Cholinesterase Inhibitors and NMDA Receptor Antagonists

8

Nazia Nazam, Aisha Farhana, and Sibhghatulla Shaikh

Abstract

Research endeavors toward Alzheimer's disease (AD) treatment target early detection, focusing on improving cognition and slowing down disease progression. The advancements achieved are credited to the increase in understanding AD at the molecular level with the combined efforts of the clinicians, researchers, and the drug industries. Thus, several medications are proven successful in ameliorating the diseased symptoms; however, none could stop or reverse disease progression. Among these, recent developments in AD therapeutics based on the "cholinergic hypothesis" and "amyloid cascade hypothesis" hold enormous treatment potential.

Keywords

Alzheimer's disease · Acetylcholinesterase inhibitors · NMDA receptor antagonist

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Abbreviations

τ protein	Tau protein
ACh	Acetylcholine
AChE	Acetylcholinesterase
AChEIs	Acetylcholinesterase inhibitors
AD	Alzheimer's disease
Apo	Apolipoprotein
Aβ peptide	Amyloid-beta peptide
APP	Amyloid precursor protein
BBB	Blood-brain barrier
BuChE	Butyrylcholinesterase
ChEIs	Cholinestrase inhibitors
Hup	Huperzine
MTDL	Multi-target-directed ligand
NFT	Neurofibrillary tangles
NMDA	*N*-methyl-D-aspartic acid
NMDAR	*N*-methyl-D-aspartic acid receptor
PS	Presenilin

8.1 Introduction

Alzheimer's disease progresses through an early synaptic dysfunction associated with an increase in the oligomeric amyloid-beta peptide (Aβ peptide). However, the etiology of AD is multifactorial and complex both in early-onset and late-onset AD, although early-onset AD is better understood to follow through gene mutations in amyloid precursor protein (APP) and presenilin (PS1, PS2) genes, finally causing unwarranted production of Aβ protein. Late-onset AD is poorly understood. The associated risk factors for late-onset AD are considered to be aging, head trauma, vascular conditions, and the presence of apolipoprotein (Apo) E4 genotype (Burns and Iliffe 2009). Pathological changes that distinctly demonstrate AD progress include anatomical lesions in the brain and senile plaques made of Aβ and neurofibrillary tangles (NFT) consisting of hyperphosphorylated tau (τ) protein, substantial loss of synapse and neuronal death, significant oxidative stress, and mitochondrial abnormalities (Perl 2010). The continual upsurge in AD cases, with higher prevalence in the geriatric population, underscores its significance as a medical concern and social burden.

8.2 Biochemical Pathways for AD Pathogenesis

Hundreds of drugs thought to improve cognition in AD efficiently have failed in clinical trials. This is highly expected since multiple biochemical pathways are at fault in AD pathogenesis, strengthening the diseased state. A single drug that could cater to all or most of the pathways would be a promising one. However, this demands an insight into the major pathways to harness essential clinical benefit. The biochemical pathways that are increasingly observed as the possible cause of Alzheimer's disease's pathogenesis align with the cholinergic hypothesis and glutamate signalling. Deterioration of cholinergic neurons and subsequent neurotransmission failure are the dominant causes of the decline in cognitive and behavioural functions observed in AD patients. Treatment strategies based on molecular knowledge of AD are currently under development. Molecular research into AD aids in identifying points of attack for rational drug treatment. Additionally, molecular markers of Alzheimers are in tremendous use comprising a part of early and differential neurochemical diagnostics.

According to the cholinergic hypothesis, a reduction in acetylcholine (ACh) synthesis is an important biochemical event in AD development (Bartus et al. 1982). Therefore, AChE is proven as the most viable therapeutic target for the symptomatic treatment of AD (Fig. 8.1). Though cholinergic drugs increase existing levels of acetylcholine to surviving brain cells, they are not completely successful in preventing neuronal death or disease progression (Raschetti et al. 2007; Forette and Hauw 2008). The reason being these drugs have positive effects for only a shorter period of approximately 1–3 years, and also cannot alter disease progression. Hence, evaluating the potential AD treatments and improving clinical management via different mechanisms are essential.

Substantial evidence favors the role of disrupted glutamate in the pathophysiology of neurodegenerative disorders including AD (Emre et al. 2014; Hynd et al.

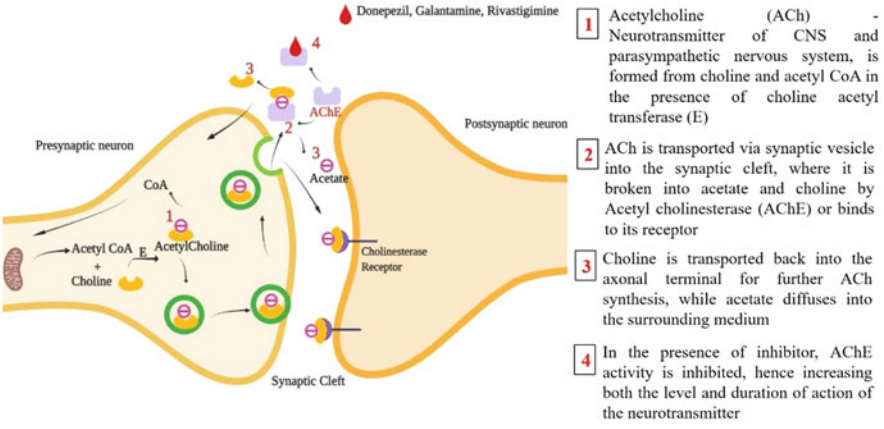

Fig. 8.1 Mechanism of action of acetylcholinesterase inhibitors in Alzheimer's disease

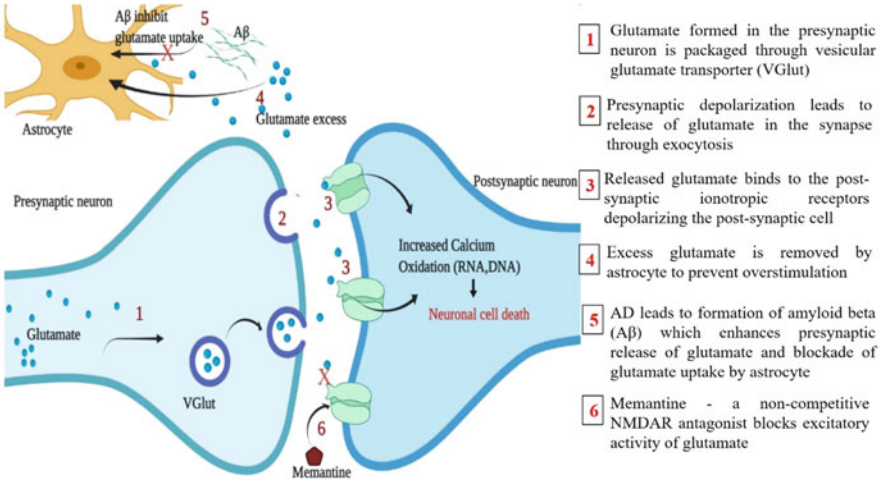

Fig. 8.2 Mechanism of action of NMDA receptor antagonist in Alzheimer's disease

2004). Glutamate is abundantly present in the CNS, as an excitatory neurotransmitter, solely located intracellularly. Extracellular concentrations of glutamate are highly regulated for appropriate signal transmission. Alzheimer's disease is associated with a higher concentration of glutamate, leading to synaptic dysfunction. High glutamate leads to membrane depolarization and opening up of *N*-methyl-D-aspartic acid (NMDA) receptors, which causes an excessive cellular influx of calcium, tilting the balance toward excitotoxicity (Zhang et al. 2016b). NMDA/mGluR-mediated Ca^{2+} influx is a crucial factor that facilitates soluble Aβ-mediated neurotoxicity resulting in amyloid plaques forming in the brain (Ferreira et al. 2015). Thus, glutamate NMDA receptor (NMDAR) antagonists have emerged as crucial therapeutic targets in AD (Fig. 8.2).

Since AD presents as a multifactorial disease, research aims to develop multi-target drugs to impede other factors such as Aβ aggregation, τ aggregation, protein misfolding, mitochondrila dysfunction, deranged metal homeostasis, decreased ACh levels, and associated oxidative stress (Fig. 8.3).

With these many therapies designed for AD, many may delay the disease progression and improve health-related quality of life, with no assurance for cure or reversal of symptoms. Presently, FDA-approved drugs comprising the mainstays for AD treatment include:

1. Cholinesterase (ChE) inhibitors.
2. NMDA glutamate receptor antagonists.

The perplexing cascades of neuronal cell death in Alzheimer's disease point to the need of in-depth investigation of potential drugs. These drugs have received FDA approval since they are a step ahead in the path of developing better treatment strategy. This chapter discusses about the spectrum of ChE inhibitors and

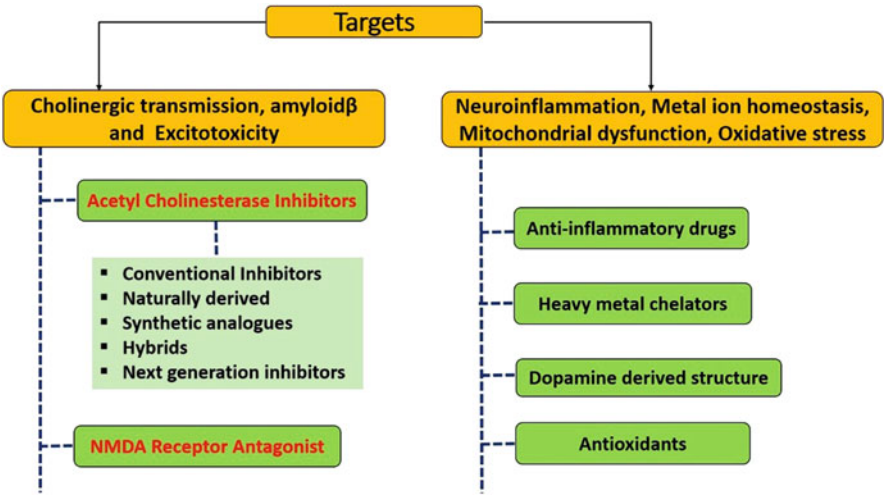

Fig. 8.3 Drugs for targeted treatment in Alzheimer's disease

NMDAR antagonist along with other treatment options used in Alzheimer's therapy. This chapter is in tune with the title of the book, which emphasizes on the recent advancements toward novel frontiers in drug discovery against AD.

8.2.1 Cholinestrase Inhibitors (ChEIs)

The α/β hydrolase is a superfamily of hydrolytic enzymes with catalytic function sharing a common "*α/β hydrolase*" fold. This hydrolase fold comprises proteases, esterases, lipases, peroxidases, epoxide hydrolases, and dehalogenases (David et al. 1992). Among the vertebrates, two types of cholinesterase enzymes are majorly found: *acetylcholinesterase (AChE)* and *butyrylcholinesterase (BuChE)*. The physiological function of both is catalyzing acetylcholine in the synapse and neuromuscular junction, finally leading to the cessation of the nerve impulse. AChE is related to butyrylcholinesterase (EC 3.1.1.8) closely, but they are distinguished from one another based on specificity for substrate, tissue distribution, and sensitivity to inhibitors (Lane et al. 2006).

ChE antagonists, also known as AChE inhibitors (AChEIs) or anticholinesterases, prevent acetylcholine breakdown by inhibiting the AChE enzyme in the cortex and hippocampus regions of the brain, which are the central foci of AD progression. Ample evidence from neuropathological and imaging studies show substantial cholinergic deficits in AD phases (Perry et al. 1993; Shinotoh et al. 2000; Bohnen et al. 2003). Such deficits in cholinergic activity call for the need of AChE inhibitors to treat cognitive and memory impairments (Shinotoh et al. 2000; van Laar et al. 2011). Improvement of cholinergic transmission could excite the cholinergic receptors or prolong ACh availability in the synaptic cleft and improve

Table 8.1 List of acetylcholinesterase inhibitors in clinical and preclinical phases

Conventional	Approved and currently in use	• Donepezil • Galantamine • Rivastigmine
	Use discontinued	• Tacrine • Physostigmine
Naturally derived	• Flavinoid (galangin, quercetin) • Phenolic lipid (cardanol) • Derived from algae and ascidians (anatoxins) • Alkaloid (Huperzine A and B) • ZT-1-A prodrug of Hup-A • Carbamates (physostigmine)	
Synthetic analogue	• Analogues of phenyl-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-2-indenylmethanone • Tacrine analogue (*N*-alkyl-7-methoxytacrine hydrochlo-ride) • 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives • Ladostigil (*N*-propargyl-(3R) aminoindan-5yl)-ethyl methyl carbamate) • 1,2,3-triazole-chromenone carboxamide derivatives • 1,2,4-triazine and Chromone scaffolds • Chalcone-based derivatives • Donepezil-based multifunctional inhibitors	
Hybrids	• Donepezil-AP2238 • Donepezil-based dual inhibitors • Tacrine based (tacrine-melatonin, gallamine-tacrine)	
Next generation	• Physostigmine derivatives (phenserine, tolserine, and eseroline) • NS2330 (tesofensine)	

AD-associated symptoms. The inhibition of cholinesterases (both acetyl and butyryl) by cholinesterase inhibitors is a promising strategy. These inhibitors targeting AChE and BuChE are approved as therapeutic strategies to alleviate AD and prevent its progression. These ChE antagonists are documented as safe, well-tolerated, and effective in slowing down cognitive impairment and neurodegeneration that may temporarily alleviate AD symptoms. The capacity of BChE is not understood well but is expected to play a role in some neurodegenerative disorders, including AD. Hence, its inhibitors could be developed in the future for improvement in AD symptoms. Noteworthy is the research focussed on AChE inhibitors, which has scaled up from potent poison (sarin, soman) of war periods to effective medicine (tacrine, donepezil) in the present peaceful days. Nevertheless, pharmacotherapy has significantly evolved, yet few drugs with promising results are presently used to prevent dementia in AD. The acetylcholinesterase inhibitors include (1) *conventional inhibitors*, (2) *naturally derived inhibitors*, (3) *synthetic analogs*, (4) *hybrid inhibitors*, and (5) *next-generation inhibitors* (Table 8.1).

8.2.2 Conventional Inhibitors

This group majorly includes the following drugs: (1) *tacrine* (Cognex: 1993), (2) *donepezil* (Aricept: 1996), (3) *galantamine* (Razadyne: 2001), and (4) *rivastigmine* (Exelon: 2002).

Prior to tacrine, physostigmine—the first classic AChEI—was investigated for AD but was later discontinued due to its poor tolerability (Thal et al. 1983). *Tacrine* (tetrahydroaminoacridine, Cognex), a nonselective, reversible AChEI, was FDA approved in 1993 and the first marketed drug for AD treatment. Its most potent acute effect on cognition is attributed to added pharmacological drug properties that include blockade of potassium channels, inhibition of monoamine uptake, and inhibition of the monoamine oxidase (Wagstaff and McTavish 1994). Tacrine, however, is no longer in clinical use for its narrow therapeutic index, frequent cases of severe hepatotoxicity, and gastrointestinal toxicity. A high incidence of cholinergic side effects, nausea and vomiting, diarrhea, dyspepsia or anorexia, and myalgia also favored its discontinuity in use (Wagstaff and McTavish 1994). Additionally, this drug was required to be administered in multiple doses due to its short half-life.

Donepezil has been used for the treatment of mild-to-moderate AD. The action of donepezil spans molecular and cellular levels to the pathogenesis of AD and not just at the neurotransmitter level. It increases the availability of ACh at the synapses, which enhances cholinergic transmission. It is also effective in inhibiting different forms of glutamate-induced excitotoxicity, lowering inflammatory cytokines, and increasing neuroprotective isoforms of AChE. Overall, donepezil helps alleviate oxidative stress and other side effects (Jia et al. 2020). The structure of donepezil allows for the synchronized inhibition of the active and the peripheral anionic sites of AChE (Kryger et al. 1999). High doses of donepezil cause severe vomiting, muscle weakness, blood pressure, nausea, breathing problems, and sometimes bradycardia (Asiri and Mostafa 2010).

Drug *galantamine* improves cholinergic function in the brain through an increase in synaptic ACh levels (Anand and Singh 2013; Andrieu et al. 2015). It was originally isolated from plants but is now chemically synthesized and is used for the treatment of AD since 2001. It is a specific, competitive, and reversible AChE inhibitor, besides binding to nicotinic cholinergic receptors. Hence, it is effective in treating the cognitive symptoms in AD patients. If administered with a gradual increase in the dosage, it showed good tolerance (Lin et al. 2019). The associated side effects include convulsions, severe nausea, stomach cramps, and vomiting (Mehta et al. 2012). In combination with memantine (a glutamate antagonist), galantamine is followed as a standard of care for AD therapy, which has provided concurrent improvement in patient symptoms (Koola 2020).

The second-generation AChEI has entered the market. Another drug, *rivastigmine tartrate*, is used to treat mild-to-moderate AD. It is proposed to exert its effect by enhancing cholinergic activity through its targets—butyryl- and acetyl-ChE. Chemically a carbamate, rivastigmine tartrate binds to AChE and is cleaved into many phenol derivatives that are rapidly excreted. The carbamate moiety of

rivastigmine binds the ES subunit of AChE with higher affinity than the acetate moiety of ACh. This binding inactivates the enzyme for a short period. Side effects of rivastigmine include stomach pain, diarrhea, nausea and vomiting, and loss of appetite. Overdosing may cause fast or slow breathing, chest pain, and slow or irregular heartbeat (Hirosawa et al. 2020). While rivastigmine and galantamine are efficacious in AD patients with mild-to-moderate symptoms, donepezil benefits are extended in alleviating severe AD symptoms (Feldman et al. 2001; Farlow et al. 2010). Galantamine, together with donepezil, also effectively inhibits AChE (Hirosawa et al. 2020). While rivastigmine is a reversible BChE and AChE inhibitor, donepezil is highly selective for acetyl compared to butyryl-ChE (Hirosawa et al. 2020).

Physostigmine is a tertiary amine carbamate AChE inhibitor, which effectively crosses the blood-brain barrier (BBB) (Hirosawa et al. 2020). However, the drug loses its therapeutic potential owing to its short half-life and adverse side effects. This has also been discontinued like tacrine due to higher side effects than their therapeutic indexes.

Though the past decades witnessed quite a few efficient AChE inhibitors, the efficacy of these drugs has been narrow and could alleviate AD symptoms for a short time (Li et al. 2019). None of them were effective in curtailing the progression of AD (Huisa et al. 2019). Furthermore, the administration of these drugs is associated with varied side effects, especially at higher doses. Innumerable short-term clinical trials; double-blind, randomized controlled trials (placebo); and long-term cohort studies highlight the following: (a) presently used AChEIs (donepezil, rivastigmine, and galantamine) decrease cognitive, functional, and behavioral deterioration in Alzheimer's disease; (b) efficacies of either of them are apparently similar; (c) benefits from them remain with treatment continuation; (d) their benefits are mostly dose-related (until limited by side effects at very high doses); and (e) they are safe and well tolerated.

Currently, natural and synthetic drug molecules are also in use for AD treatment, of which some are in clinical use currently or in clinical trials based on accepted treatment strategies. Naturally derived inhibitors are identified and isolated natural molecules such as polyphenols, carbamates, alkaloids, and anatoxins (from green algae). At the same time, synthetic analogs include indenyl derivatives, ladostigil, and tacrine analogs.

8.2.3 Naturally Derived Inhibitors

Numerous phytochemical studies have identified and isolated natural molecules such as alkaloids, coumarins, terpenes, and polyphenols possessing a wide range of pharmacological activity against cholinesterase enzymes. These natural products also possess antioxidant, anti-inflammatory, anti-amyloidogenic, and neuroprotective activities. Hence, they have been assessed for designing and developing new anti-Alzheimer's drugs (Huang et al. 2014b).

Flavonoids have served as a good candidate as an AD inhibitor due to their free-radical-scavenging characteristics. Many derivatives of flavonoids, such as quercetin and galangin, have shown efficacy in AChE inhibition (Uriarte-Pueyo and Calvo 2011). Similarly, cardanol, a phenolic lipid extracted from cashew nut shells, has shown promising results in inhibiting AChE (Lemes et al. 2016). However, the toxicity and side effects for both compounds have not been evaluated in preclinical or clinical settings. Some cholinesterase inhibitors derived from marine sources such as algae and ascidians have also proven to inhibit AChE activity (Moodie et al. 2019). Recently, honey has been demonstrated in a preliminary study as a source of AChE inhibitors attributed primarily to its flavonoids and phenolic acid content (Baranowska-Wójcik et al. 2020).

The lesser use of Huperzine A (HupA), again a natural AChE inhibitor for AD patients' clinical treatment, is reported. Its property of being a highly selective, reversible, and potent AChE inhibitor gained attention (Wang et al. 2009). HupA when hybridized with donepzil has resulted in lesser effectiveness. While the HupA-tacrine hybrids known as Huprines Y and X are potent in inhibiting AChE in vitro compared to Tacrine (Camps and Munoz-Torrero 2005). HupA alone with its higher oral bioavailability than tacrine and donepezil shows appreciable improvement on working memory than reference memory (Bai 2007). HupA is better in inhibiting AChE activity than tacrine, rivastigmine, and galantamine with the least activity against BuChE (Wang et al. 2009). Huperzine B (HupB) is another natural alkaloid isolated from lycopodium proven effective and a reversible inhibitor of AChE. However, HupB is not that potent and selective like HupA, but it has a greater therapeutic index and other encouraging benefits (Bai 2007).

Nonetheless, the global availability of HupA tossed with greater potency prevents the clinical development of HupB. Yet the clinical use of HupA for AD treatment is lesser because of its sale in the USA as a nutraceutical supplement. This is due to the lack of a proprietary patent, and hence, FDA approval is not being pursued.

8.3 Synthetic Analogs: Indenyl Derivatives, Tacrine Analog, Donepezil-Based Derivatives

Targeted drug analogs such as indenyl derivatives, ladostigil, and tacrine analogs have been used in the treatment regime for AD. Though they bypass the gastrointestinal side effects and hepatotoxicity, they have lower BBB permeability leading to lower efficacy as compared to other types of AChEIs.

Numerous researchers found that analogs of phenyl-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-2-indenylmethanone show moderate AChE inhibitory effects suggesting the presence of methoxy groups on the phenyl ring plausibly improved the inhibition of AChE (Ali et al. 2009; Gupta and Patil 2020). Tacrine analog *N*-alkyl-7-methoxytacrine hydrochloride has shown enhancement in the AChE-inhibitory potential more than the parent drug tacrine (De La Torre et al. 2012). Another set of synthetic analog, 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives, has been proposed to treat AD, which showed inhibition of AChE at

nanomolar concentrations (Taslimi et al. 2020). Ladostigil, *N*-propargyl-(3R) aminoindan-5yl)-ethyl methyl carbamate, was evaluated to provide potent inhibition of AChE together with neuroprotective properties (Albertini et al. 2020). The drug combines the neuroprotective effects of rasagiline, a selective monoamine oxidase (MAO)-B inhibitor, used for Parkinson's disease with AChE inhibitory activity of rivastigmine, as a potential AD drug (Yogev-Falach et al. 2006). It is presently in Phase II clinical trials. Also, 1,2,3-triazole-chromenone carboxamide derivatives and 1,2,4-triazine and chromone scaffolds are developed as a multi-target agent for AD treatment (Rastegari et al. 2019; Mohsin et al. 2020). Chalcone-based derivatives have also been evaluated to demonstrate AChE inhibitory properties (Burmaoglu et al. 2020). Donepezil-based multifunctional derivatives are also under evaluations as AChE inhibitors to treat AD (Li et al. 2018).

Multifactorial AD pathogenesis suggests controlling one target as insufficient in AD therapy. This could be overcome with a new emerging strategy named multi-target-directed ligands (MTDLs) (Bolognesi et al. 2008), wherein one compound as a hybrid molecule simultaneously aims diverse targets with close association to AD (Bajda et al. 2011). Numerous researchers have focused on developing donepezil-based multifunctional ChEI for AD treatment due to its dual-site inhibition property (Li et al. 2016, 2018; Cao et al. 2020). Various indinone derivatives have shown anti-cholinesterase properties (Huang et al. 2014a; Guzior et al. 2014).

8.3.1 Hybrid Inhibitors

For a multifactorial disease like AD, the state-of-the-art model is of the "single-ligand, multiple-target" approach. Hybrids combine BBB permeability with drugs targeting multiple receptors, promising dual mode of action and enhanced effectiveness. Donepezil-AP2238 hybrid was the first developed drug with dual binding sites (Piazzi et al. 2003). Though similar in activities, the effect of AP2238 in inhibiting Aβ-mediated toxicity is higher than donepezil (Piazzi et al. 2003). Currently, the side effect profiles in humans for these hybrids are not known. Drugs used to target aggregation of Aβ protein and AChE activity such as donepezil-based dual inhibitors and tacrine hybrids have been used to target both Aβ aggregation and AChE inhibition (Camps et al. 2008; Tang et al. 2011; Zhang et al. 2016a). Other multipotent hybrid inhibitors include novel tacrine-melatonin hybrids, dual inhibitors of AChE and monoamine oxidase or serotonin transporters, potent ChEIs with antioxidant neuroprotective properties, gallamine-tacrine hybrids binding at ChE, and muscarinic receptors (Singh et al. 2016). The curative model of one-ligand one-target followed from so many decades should now move toward single-molecule targeting as many factors or pathways involved in neuronal death.

8.3.2 Next-Generation Inhibitors

The derivatives of physostigmine such as tolserine, eseroline, and phenserine, have been synthesized and tested for its activity on AChE. Tolserine differs from phenserine at the phenylcarbinol moiety, by the presence of a 2-methyl group. This provided tolserine a 200-fold selectivity toward human AChE compared with BChE, which is active at lower concentrations than physostigmine (Kamal et al. 2000). It also showed increased potency toward AChE compared to phenserine or physostigmine (Yu et al. 2010). Another drug, eseroline, a metabolite of physostigmine, was effective against ACE with higher selectivity than BChE (Zhan et al. 2010). However, the drug has not been continued to be used for AD therapy.

A selective, noncompetitive AChE inhibitor, Phenserine, has been shown to improve cognition in AD patients. Phenserine also reduces the APP mRNA, reducing Aβ peptide formation (Zhan et al. 2010). Clinical testing for AD showed only moderate success in initial Phase II clinical trials. Phenserine was considered a promising drug for developing novel strategies for AD treatment because of its dual effects. However, some Phase III clinical trials indicated it as ineffective, while another clinical trial indicated its effectiveness at higher doses (Becker et al. 2018). Nonetheless, clinical investigations with phenserine are still underway (Lecca et al. 2019).

Another new AChE inhibitor—NS2330 (tesofensine)—was observed to enhance acetylcholine function both in in vitro and in vivo studies (Lehr et al. 2007). Promising results were obtained in the Phase IIA trials showing substantial cognitive improvement in patients with mild AD. But, Phase IIB trials revealed restricted activity; hence the trials did not continue beyond 2007 (Lehr et al. 2007).

In a nutshell, AChEIs alter AD's clinical indicators, and the therapy results in a modest but significant cognitive effect in AD. An alternative approach to treating Alzheimer's disease is the inhibition of NMDA glutamate receptors, which is thought to lead to less excitotoxic injury to the brain.

8.4 *N*-Methyl-D-aspartate (NMDA) Receptor Antagonist

The single NMDA receptor inhibitor approved for use in Alzheimer's disease is the glutamate antagonist *memantine* (Namenda: 2003). Memantine has been widely used with modest benefits in clinical settings for the symptomatic treatment of moderate-to-severe forms of AD (Agüera-Ortiz 2010). Memantine being one such antagonist modulates the flow of glutamatergic neuronal transmission relying on glutamate as the main excitatory neurotransmitter. During normal physiological functions, memantine ineffectively blocks the low receptor activity levels. While at enhanced glutamate concentrations associated with increased activation of NMDAR, it is found to be appreciably effective (Chen and Lipton 2006) and, hence, blocks the lethal effects of overactive glutamatergic activity such as compromised synaptic plasticity and neuron damage (Danysz and Parsons 2003). Better benefits to the patients were harnessed when memantine is used along with

AChE inhibitors. Notably, memantine being well tolerated in AD, its combination with other therapies could be a valuable and feasible alternative. And in numerous clinical trials, it has displayed statistically significant improvements (Van Dyck et al. 2007). Thus, it is concluded that NMDAR antagonists hold potential in the upcoming treatments of this neurodegenerative disorder.

8.5 Other Treatment Options

Another major drug approach is to target tau protein hyperphosphorylation causing the formation of intracellular neurofibrillary tangles of the microtubule-associated τ protein (Panza et al. 2016; Hashweh et al. 2020). With the discovery of phenothiazines and methylthioninium as τ protein aggregation inhibitors, computational analysis-based drug discovery has speeded up. Many additional small molecule inhibitors have been discovered, and studies were carried out to identify effective inhibitors. Nonetheless, an effective inhibitor should have improved blood-brain barrier permeability and milder side effects. Presently, many clinical trials are being carried out on drugs that target earlier stages of the disease, particularly preclinical AD instead of mild-or-moderate disease (Khoury et al. 2017).

8.6 Future Directions

With the discovery of first acetylcholinesterase inhibitor—physostigmine—numerous studies have been done to gain better and efficient inhibitors (Thal et al. 1983). Compared to the traditional inhibitors, their analogs, naturally derived inhibitors and hybrid of synthetic inhibitors, cause less side effects. They also bear enhanced properties such as improved BBB permeability and better efficacy (Camps et al. 2008). Studies on most of these inhibitors are either on animal models or done in vitro and computational based. Hence, to ascertain their safety, toxicity, and efficacy, future studies are needed in humans. Single drug agent is inefficient in inhibiting disease progression completely, and undoubtedly many of such single target agents have failed in clinical trials. Hence, a multi-target-directed ligand is a wise approach with promising results toward various abnormalities, symptoms, and pathways. For prospective studies, the design of novel MTDLs should bear the characteristics based on available structure-activity relationship studies (Luo et al. 2013; Zhang et al. 2018; Singh et al. 2019).

Nonetheless, extensive randomized studies and more clinical trials of such inhibitors are required to evaluate their potential and confirm their specific role. The choice among drug combinations should be based on safety, drug burden, drug-drug interactions, and a total number of non-overlapping pathways targeted. Clinical trials should test the efficacy and safety of the drug combinations for which promising research and clinical studies are available. Investigations in the future need to correlate patient's response to clinically vital outcomes that can streamline benefits out of these drugs as single agent, combination, or MTDLs.

8.7 Conclusions

Globally accepted anti-Alzheimer drug therapy comprises four acetylcholinesterase inhibitors (tacrine, donepezil, rivastigmine, and galantamine) and one NMDA receptor antagonist (memantine). All of them are more palliative than disease-modifying therapy, and hence, none of them are successful in preventing the final disease outcome. Acetylcholinesterase inhibitor-based investigations and the progress have scaled up from neurotoxins to neuroprotection characterized by cholinergic deficit in AD. The clinical trials in this direction have confirmed appreciable improvements in cognition and activities of daily living with these modulators. Yet not all AD sufferers are benefitted from these existing therapeutics. Currently, existing drug therapies are associated with several side effects; hence developing novel agents with different structures and action modes is needed. Being a multifactorial disease, multi-target inhibitors for Alzheimer's are a promising alternative. Simultaneously addressing many biochemical pathways could stall this multifactorial disease by hindering the cognitive impairment in the first place. Additionally, the impact of treatment on long-term outcomes, including institutionalization, remains unclear. Also, evidence supporting a duration for which these treatments should be given is limited (Glynn-Servedio and Ranola 2017).

The elderly population is enormously expanding, and it is speculated that by 2050, one in three persons will have dementia, mainly due to Alzheimer's disease (Glynn-Servedio and Ranola 2017). This demands developing effective ways for very early diagnosis and efficient disease-modulating therapies to avert and treat AD. Overall, more significant efforts are needed to gain insight into the disease mechanism and discover new scaffolds with novel drug targets, better drug efficacy, safety, and prolonged adequate time. With the advancement in understanding inhibitors and antagonists, preclinical markers and neuropreventive strategies should also be targeted toward "at-risk" patients before the disease's clinical onset.

Conflict of Interest The authors declare no conflict of interest.

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Genetic Basis of Psychotic Illnesses: A Comprehensive Overview

9

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Abstract

Psychotic illness is a major health burden at the present world. Common psychotic disorders like autism spectrum disorders and schizophrenia frequently share clinical manifestations caused by brain dysfunction. However, there is a clear distinction between early- and late-onset psychotic illnesses. Despite appreciable advancement in identifying the genetic risk factors for most psychiatric illnesses, it is still unknown how these genetic variants interact with epigenetic risk factors and environmental factors that predispose risk for these clinically distinct disorders. In this chapter, we tried to trace the clinical features of psychotic illnesses and the relationship between these disorders with genetic insight. Furthermore, we reviewed the common therapeutic targets for these conditions. From the discussion, it is clear that psychotic illnesses share a genetic overlap and the therapeutic target of these abnormalities relies on the same pipeline. Therefore, prospects will be to develop more specific therapies for treating psychotic illnesses.

Keywords

Psychotic illness · Autism spectrum disorders · Schizophrenia · Childhood-onset schizophrenia · Multiplex developmental disorder · Genetic factors · Oxytocin

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9.1 Introduction

Psychotic illness is a combined period of unusual perceptions termed hallucinations and distortions of reality called delusions. The prevalence of psychotic illness is relatively low in the world's general population, comprising a ratio of about 1:100. However, increased research on psychotic disorders has revealed a higher frequency of this disorder. For instance, recent data suggest that psychotic disorder is found in more than 3 in every 100 autistic people, which is almost three times higher than in the general population (Zheng et al. 2018).

There is a substantial overlap between different psychotic conditions describing the relationship between them. The complex relationship of autism spectrum disorder (ASD) and schizophrenia is one such case (King and Lord 2011). However, these disorders may vary considerably in terms of age of onset, with the former usually first seen in childhood and the latter in adolescence or early adulthood. Moreover, people with ASD may present comorbid psychotic conditions, including schizophrenia and bipolar disorder. This ultimately predisposes a person with ASD to a greater risk of experiencing psychotic disorders than the general population (Larson et al. 2017).

The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) classified ASD under neurodevelopmental disorders and schizophrenia under schizophrenia spectrum and other psychotic disorders of section II (Regier et al. 2013). According to a previous study performed by Pourcain et al. (2018), the shared genetic causes between various psychiatric illnesses found a slight overlap between ASD and schizophrenia. However, a more significant overlap was observed than adult-onset psychiatric disorders. Mouridsen et al. (2008) reported that the rate is as high as 28%. A population-based study demonstrated that depending on the type of psychotic illnesses, ASD patients with their odds have a comorbid psychotic illness between 5.6 and 5.8 (Selten et al. 2015). Another previous study has also described the epidemiological evidence about the connection between childhood developmental disorders and adulthood psychotic conditions (Khandaker et al. 2014).

In this chapter, we try to trace the clinical features of various psychotic illnesses such as ASD, schizophrenia, and the relationship between these disorders with genetic insight. Furthermore, we overview the common therapeutic targets and provide prospects of these conditions.

9.2 Clinical Features Shared Between Psychotic Disorders

From the very beginning, it has been a common debate in the thought of psychiatric diseases whether or not the association between various disorders exists. Are there any relations among these abnormalities, for example, if autism shares its features with schizophrenia or it is distinct? Suppose we try to get the origin of this debate. In that case, we have to look back to the history of the clinical discoveries and

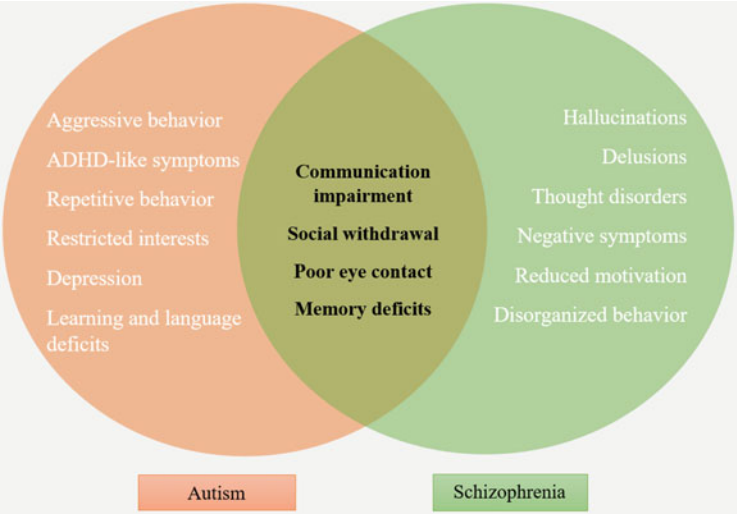

Fig. 9.1 Shared clinical features between ASD and schizophrenia

phenomenological manifestations from the past century of these disorders (Vorstman and Burbach 2014).

However, recent results from thousands of genetic studies have revitalized the concept by providing more recent insights into the genetic risk factors for psychiatric disorders like ASD, schizophrenia, or others (Vorstman and Burbach 2014).

Although psychiatric illnesses are distinct, they share some common clinical characteristics. For instance, impairment of communication, poor eye contact, and social withdrawal faced by ASD patients are almost similar to symptoms (negative) of schizophrenia in youths, as shown in Fig. 9.1 (Posey et al. 2004). From a study by the National Institute of Mental Health (NIMH), it was found that a subset of children (28%) with childhood-onset schizophrenia (COS) have comorbid COS and ASD (Rapoport et al. 2009).

Surprisingly, some experiments have followed ASD individuals forward into adulthood or looked back in schizophrenic adults for consistent ASD history. A study confirms a relatively stronger correlation between ASD and schizophrenia than what is assumed from their respective prevalence. According to earlier reports, around 12% to 50% of individuals with ASD face psychotic disorders (Sverd 2003). Other studies also confirmed subgroup overlapping between psychotic conditions. Konstantareas and Hewitt (2001) reported that all ASD patients with similar criteria as schizophrenia suffered from disorganized subtype, though patients with paranoid schizophrenia experienced ASD.

Moreover, male patients with ASD experienced a higher frequency of negative symptoms than those with schizophrenia, which is related closely to the deficit subtype of schizophrenia. An investigation by Stahlberg et al. (2004) concluded that around 50% of patients from 241 adults with childhood neuropsychiatric

disorders had ASD when they were assessed without exclusion criteria. Among them, 15% of adults met the criteria for psychotic disorders.

Most researchers use different terms to describe psychiatric comorbidities and developmental psychopathology due to mixed or shared clinical features. For example, researchers from Yale Child Study Center named a subgroup of ASD children as "multiplex developmental disorder" (MCDD) (Towbin et al. 1993; Klin et al. 1995), which the researchers of Netherlands further applied to describe children meeting similar criteria for both ASD and disordered thinking and/or affect dysregulation (van der Gaag et al. 1995, 2005; Buitelaar and van der Gaag 1998; de Bruin et al. 2007). A follow-up study by van der Gaag et al. (1995) found that psychotic illness is developed by adulthood in almost 64% of children with MCDD. A similar study compared youths at risk for psychotic disorders and youths with MCDD but found no differences in schizophrenic characteristics, disorganization, or prodromal symptoms.

However, in terms of early development and treatment histories, both groups had apparent differences. The study explicated that most of the children with MCDD are at high risk for the development of psychotic illness in the latter half of their life. Almost 78% of the MCDD group met the criteria for at-risk mental condition (Sprong et al. 2008).

9.3 Genetics Behind Psychotic Disorders

Despite appreciable advancement in identifying the genetic risk factors or etiology for most psychiatric illnesses, it is still unknown how these genetic variants interact with epigenetic risk factors and environmental factors that predispose risk for clinically distinct disorders. Several studies demonstrated that shared genetic factors might underlie a substantial part of cross-disorder expression overlap in individuals (Geschwind and Flint 2015; Gandal et al. 2016; Gandal et al. 2018).

Various studies have reported multiple genes that are associated with ASD as shown in Table 9.1 (Wiśniowiecka-Kowalnik and Nowakowska 2019; Rylaarsdam and Guemez-Gamboa 2019; Matsuzaki et al. 2012) and schizophrenia as shown in Table 9.2 (Lin et al. 2016; Escudero and Johnstone 2014). Notably, many potential candidate genes of ASD are associated with other psychiatric disorders, specifically, schizophrenia, describing a genetic overlap between ASD and schizophrenia (Table 9.3) (Rapoport et al. 2009; Crespi et al. 2010; Kasarpalkar et al. 2014; Lin et al. 2016; Cross-Disorder Group of the Psychiatric Genomics Consortium 2013). This overlap is found not only for schizophrenia but also in other neuropsychiatric disorders such as mental retardation or attention deficit hyperactivity disorder (ADHD) (Vorstman and Burbach 2014). Researches with polygenic risk scores have consistently shown that mental disorders' prediction improves by including genetic variants that are more weakly associated. This data suggests that thousands of genetic variants are associated with determining the risk for most psychotic illnesses (Wray et al. 2014).

Table 9.1 Candidate gene for autism spectrum disorder (ASD)

Gene	Description	Chromosomal location
ABCA1	ATP binding cassette subfamily A member 1	9q31.1
ADNP	Activity-dependent neuroprotector homeobox	20q13.13
ANK3	Ankyrin 3	10q21.2
ATP10C	ATPase class V type 10C	15q12
CACNA1E	Calcium voltage-gated channel subunit alpha1 E	1q25.3
CADPS2	Ca^{2+}-dependent secretion activator 2	7q31.32
CHD8	Chromodomain helicase DNA binding protein 8	14q11.2
CLCN6	Chloride voltage-gated channel 6	1p36.22
DLX5	Distal-less homeobox 5	7q21.3
EFHC2	EF-hand domain (C-terminal) containing 2	Xp11.3
FMR1	Fragile X mental retardation 1	Xq27.3
FOXP1	Forkhead box P1	3p13
FOXP2	Forkhead box P2	7q31.1
GABRB3	Gamma-aminobutyric acid A receptor, beta 3	15q12
GABRG3	Gamma-aminobutyric acid type A receptor Gamma 3 subunit	15q12
GRIN2B	Glutamate ionotropic receptor NMDA type subunit 2B	12p13.1
HOXA1	Homeobox A1	7p15.2
HTR3A	5-hydroxytryptamine receptor 3A	11q23.2
IMMP2L	IMP2 inner mitochondrial membrane peptidase-like	7q31.1
KATNAL2	Katanin catalytic subunit A1 like 2	18q21.1
KCND2	Potassium voltage-gated channel subfamily D member 2	7q31.31
KCNQ3	Potassium voltage-gated channel subfamily Q members 3	8q24.22
KCNQ5	Potassium voltage-gated channel subfamily Q members 5	6q13
NLGN3	Neuroligin 3	Xq13.1
NRP2	Neuropilin 2	2q33.3
POGZ	Pogo transposable element derived with ZNF domain	1q21.3
RBFOX	RNA binding forkhead box	16p13.3
RIPK2	Receptor interacting serine/threonine kinase 2	8q21.3
SCN2A	Sodium voltage-gated channel alpha subunit 2	2q24.3
SHANK2	SH3 and multiple ankyrin repeat domains 2	11q13.3-q13.4
SHANK3	SH3 and multiple ankyrin repeat domains 3	22q13.33
SLC6A4	Serotonin transporter; solute carrier family 6 member 4	17q11
SNRPN	Small nuclear ribonucleoprotein polypeptide N	15q11.2
SYN1	Synaptic vesicle cycling proteins synapsin-1	Xp11.3-p11.23
SYN2	Synaptic vesicle cycling proteins synapsin-2	3p25.2
SYNGAP1	Synaptic Ras GTPase activating protein 1	6p21.32
TSC2	TSC complex subunit 2	16p13.3
UBE3A	Ubiquitin protein ligase E3A	15q11.2
WNT2	Wingless-type MMTV integration site family member 2	7q31.2

Table 9.2 Candidate genes for schizophrenia

Gene	Description	Chromosomal location
ADD1	Adducin 1	4p16.3
ANK3	Ankyrin 3	10q21.2
CCL22	Chemokine, CC Motif, Ligand 22	16q21
CD14	Cluster of differentiation 14	5q31.3
CD34	Hematopoietic progenitor cell antigen	1q32.2
CSMD1	CUB and Sushi multiple domains 1	8p23.2
CXCL12	Chemokine, CXC Motif, Ligand 12	10q11.21
DOCK4	Dedicator of cytokinesis 4	7q31.1
DPP4	Dipeptidyl peptidase IV	2q24.2
EGR1	Early growth response 1	5q31.2
FGFR1	Fibroblast growth factor receptor 1	8p11.23
FLNA	Filamin A	Xq28
FMR1	FMRP translational regulator 1	Xq27.3
GCA	Grancalcin	2q24.2
GNAL	G protein subunit alpha L	18p11.21
GRIA1	Glutamate ionotropic receptor AMPA type subunit 1	5q33.2
GRIN2A	Glutamate ionotropic receptor NMDA type subunit 2A	16p13.2
GRM3	Glutamate metabotropic receptor 3	7q21.11-q21.12
HBEGF	Heparin-binding egf-like growth factor	5q31.3
HTR3B	5-hydroxytryptamine receptor 3B	11q23.2
LRP1	Low density lipoprotein receptor-related protein 1	12q13.3
MAPK3	Mitogen-activated protein kinase 3	16p11.2
MCL1	Myeloid cell leukemia sequence 1	1q21.2
MIR137	MicroRNA 137	1p21.3
MLC1	Modulator of VRAC current 1	22q13.33
MMP16	Matrix metalloproteinase-16	8q21.3
NEURL	Neuralized E3 ubiquitin protein ligase	10q24.33
NISCH	Nischarin	3p21.1
NMUR2	Neuromedin U receptor 2	5q33.1
OPN1LW	Opsin 1, long-wave-sensitive	Xq28
PAM	Peptidylglycine alpha-amidating mono-oxygenase	5q21.1
PCGEM1	Prostate-specific transcript	2q32.3
PLA2G15	Phospholipase A2 group 15	16q22.1
PRKCD	Protein kinase C, delta	3p21.1
PRKD1	Protein kinase D1	14q12
PRMT1	Protein arginine methyltransferase 1	19q13.33
RAD51	Recombinase	15q15.1
SREBF1	Sterol regulatory element-binding transcription factor 1	17p11.2
SRR	Serine racemase	17p13.3
STAR	Steroidogenic acute regulatory protein	8p11.23
SV2B	Synaptic vesicle glycoprotein 2B	15q26.1

(continued)

Table 9.2 (continued)

Gene	Description	Chromosomal location
TAP1	Transporter, ATP-binding cassette, major histocompatibility complex, 1	6p21.32
TIE1	Tyrosine kinase with immunoglobulin and EGF factor homology domains 1	1p34.2
TPR	Translocated promoter region	1q31.1

Table 9.3 Common genes for ASD and schizophrenia

Gene	Description	Chromosomal location
APBA2	Amyloid-beta A4 precursor protein-binding family A member 2	15q13.1
AS3MT	Arsenic (+3 oxidation state) methyltransferase	10q24.32
BDNF	Brain-derived neurotrophic factor	11p14.1
CACNB2	Calcium voltage-gated channel auxiliary subunit beta 2	10p12.33-p12.31
CASPR2	Contactin-associated protein-like 2	7q35-q36
CNTNAP2	Contactin associated protein-like 2	7q35-q36.1
DAO	D-amino acid oxidase	12q24.11
DISC1	Disrupted in schizophrenia 1	1q42
DRD2	Dopamine receptor D2	11q23.2
GAD1	Glutamate decarboxylase 1	2q31.1
GRIK2	Glutamate Ionotropic Receptor Kainate Type Subunit 2	6q16.3
GSTM1	Glutathione S-transferase, MU-1	1p13.3
HTR2A	5-hydroxytryptamine receptor 2A	13q14.2
ITIH3	Inter-alpha-trypsin inhibitor, heavy chain 3	3p21.1
MAOA	Monoamine oxidase A	Xp11.3
MECP2	Methyl-CpG-binding protein 2	Xq28
MTHFR	Methylenetetrahydrofolate reductase	1p36.22
NLGN4	Neuroligin 4	Xp22.32-p22.31
NRXN1	Neurexin 1	2p16.3
RELN	Reelin	7q22.1
SLC6A3	Solute carrier family 6 member 3	5p15.33
TPH2	Tryptophan hydroxylase 2	12q21.1

The genetic relationship between ASD and schizophrenia is not studied extensively, but evidence suggests shared genetic factors (Carroll and Owen 2009). In most psychiatric illnesses and other common abnormalities, genetic complexity is often compounded by phenotypic complexity. Studies of copy number variant (CNV) and rare allele have reported a correlation between ASD and point and structural mutations in neuroligins, neurexins, and related genes (Rapoport et al. 2009). Several reports have implicated the neurexin gene family in schizophrenia. Again, neuroligins are from the postsynaptic protein family that transsynaptically interact with neurexins (presynaptic proteins) required for excitatory and inhibitory

synapses formation and maturation. This gene accumulates neurodevelopmental imbalance in both excitatory and inhibitory transmission theory for ASD and schizophrenia (Carroll and Owen 2009). Rapoport et al. (2009) showed that COS is preceded by and comorbid with a pervasive developmental disorder (PDD) in 30 to 50% of cases and average intelligence with schizophrenia in 46 patients; criteria for ASD were fulfilled by 52% of subjects, increasing to 60% in the paranoid subgroup (Unenge Hallerback et al. 2012).

Multiple deletions such as 1q21.1, 22q11.2, and 15q13.3 are associated with different psychotic disorders, including ASD, schizophrenia, ADHD, and mental retardation (Carroll and Owen 2009). The rate of ASD is higher in patients with velocardiofacial syndrome (22q11) (Vorstman et al. 2006). Similarly, microdeletions or microduplications of 16p11.2 have been observed in 1% of ASD cases and 2% of NIMH childhood-onset schizophrenia cohort (Walsh et al. 2008; Kumar et al. 2008; Shen et al. 2010). These CNVs increase the risk for a wide variety of neurodevelopmental phenotypes, including ASD and schizophrenia (Carroll and Owen 2009). Although genome-wide association studies have not shown any systemic comparisons of ASD and schizophrenia, few functional correlations have been found at voltage-gated calcium channel genes, which are associated with presynaptic neuronal function as well as neuronal plasticity across different phenotypes (Carroll and Owen 2009). Genetic changes leading to psychotic illnesses are shown in Fig. 9.2.

Almost all types of psychological disorders have shown the possibility to transfer from generation to generation, and the risk of developing a disorder depends on the type of biological relationship to the affected persons suggesting a strong genetic correlation (Gottesman et al. 2010; Rasic et al. 2014). For instance, monozygotic twins can share 100% of their nuclear deoxyribonucleic acid (DNA). They are highly concordant with each psychological abnormality compared with dizygotic twins, who share half of their genetic material. This variation indicates that psychotic illness is mainly attributable to genetic factors. Moreover, there is a gradient contribution of genetics, estimating a more significant inheritance for more severe and less common illnesses like ASD, schizophrenia, and bipolar disorder (Polderman et al. 2015). To be specific, approximately two-thirds of the genetic associations are frequent to these psychotic disorders, and overlap of genetic variants is found to contribute to the risk of ASD, ADHD, and intellectual disabilities (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013).

9.4 Common Therapeutic Targets for Psychotic Disorders

The analysis indicates that common pharmacotherapeutic targets for psychotic disorders such as ASD, schizophrenia, and others will be in the same pipeline. Multiple studies have suggested that the functional imbalance of excitatory-inhibitory transmission in ASD offers great insight into drug development (Gogolla et al. 2009; Krueger and Bear 2011). According to Kehrer et al. (2008), the development of therapeutic targets would be the same neurotransmission system

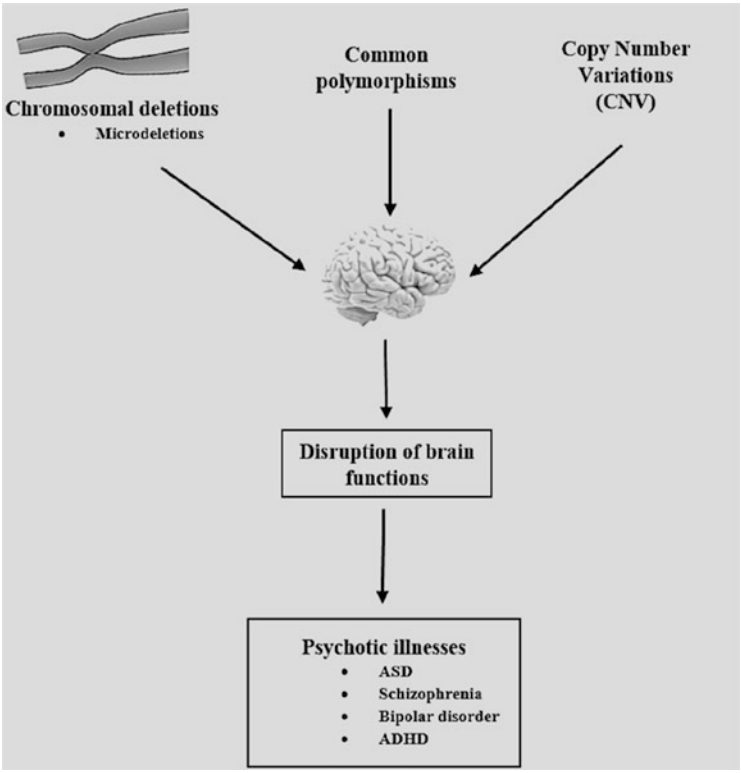

Fig. 9.2 Genetic alterations leading to psychotic illnesses

(excitatory-inhibitory) for schizophrenia. The interest in glutamatergic therapeutics targeting glutamatergic-signaling pathways also increases (King and Bostic 2006; Karam et al. 2010). Therapeutic drugs targeting gamma-aminobutyric acid (GABA)-ergic system dysfunctions also get high priority for both ASD and schizophrenia (Chattopadhyaya and Cristo 2012; Coghlan et al. 2012).

Antipsychotic medications have been the major attraction to the researchers due to their highest efficacy in treating psychotic disorders like ASD. Risperidone and aripiprazole are two US Food and Drug Administration (USFDA)-approved drugs to treat significant behavioral disturbance in autism. Surprisingly, these two drugs were initially developed for the treatment of schizophrenia. A study suggested that antipsychotic drugs improve social cognition in schizophrenia patients though the outcomes have not been tested in ASD, where the main focus is to improve behavioral disturbance (Roberts et al. 2010).

Oxytocin (OXT), a neuromodulator, is another shared therapeutic target associated with social behaviors, memory for social information, empathy, and protective silencing of the fetus's cortex at birth. It is important for social bonding and social learning, which takes place during language learning. Both oxytocin

receptor (OXTR) and OXT genetic variations are well established in ASD and schizophrenia (Ebstein et al. 2012; Montag et al. 2012) due to promising response to oxytocin such as psychotic illnesses, decreased repetitive behaviors, negative symptoms, improved recognizing abilities, and social cognitive feature (Hollander et al. 2003; Guastella et al. 2010; MacDonald and Feifel 2012).

9.5 Conclusion

Psychotic illness is a major burden to the present world. Some common psychiatric disorders like ASD and schizophrenia frequently share clinical manifestations caused by brain dysfunction. However, the distinction between early- and late-onset psychotic illnesses in children results in both disorders. Many genetic factors have been identified to be associated with these disorders. From the discussion of this chapter, it is clear that these two disorders also share a genetic overlap. Besides, the therapeutic target of these abnormalities relies on the same pipeline. Therefore, prospects will be to develop more specific therapeutic targets to treat different psychotic illnesses.

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RNA Secondary Structures in Neurodegeneration

10

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Abstract

RNA is hierarchically organized, and its 3D structure can be described at different levels. Instead of the long helices formed by two perfectly complementary strands of DNA, an RNA chain folds back on itself to form short stretches of helical regions interrupted by bulges, internal loops, hairpin loops, or multi-way

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junctions. While RNA plays a significant role in several biological processes, including translation, catalysis, and gene regulation, the RNA secondary structure's prediction is crucial for the identification and formulation of the RNA functionality. The second level of RNA hierarchical structure is RNA acting as a key factor in the posttranscriptional regulation and the noncoding RNA functions. This chapter reviews the representation, visualization, and mathematical formulation mostly of RNA secondary structures, which can be viewed as steps toward the three-dimensional prediction modeling and their role in neurodegeneration.

Keywords

Complexity · Dynamic programming · lncRNAs · Neurodegeneration · Prediction · RNA secondary structures

10.1 Introduction

The latest RNA secondary structure prediction methods include comparative sequence analysis and folding algorithms (Singh et al. 2019). Several dynamic programming tools (Akutsu 2000) are published that predict RNA secondary structures with pseudoknots or noncanonical base pairs using alternative mathematical and biophysical representations (Nowakowski and Tinoco 1997; Stein and Waterman 1978; Westhof and Fritsch 2000; Nebel 2001; Jiang et al. 2002; Reeder and Giegerich 2004; Do et al. 2006; Parisien and Major 2008; Sato et al. 2009; Schroeder 2009; Bellaousov and Mathews 2010; Reuter and Mathews 2010; Lorenz et al. 2011; Sato et al. 2011; Zakov et al. 2011; zu Siederdissen et al. 2011; Seetin

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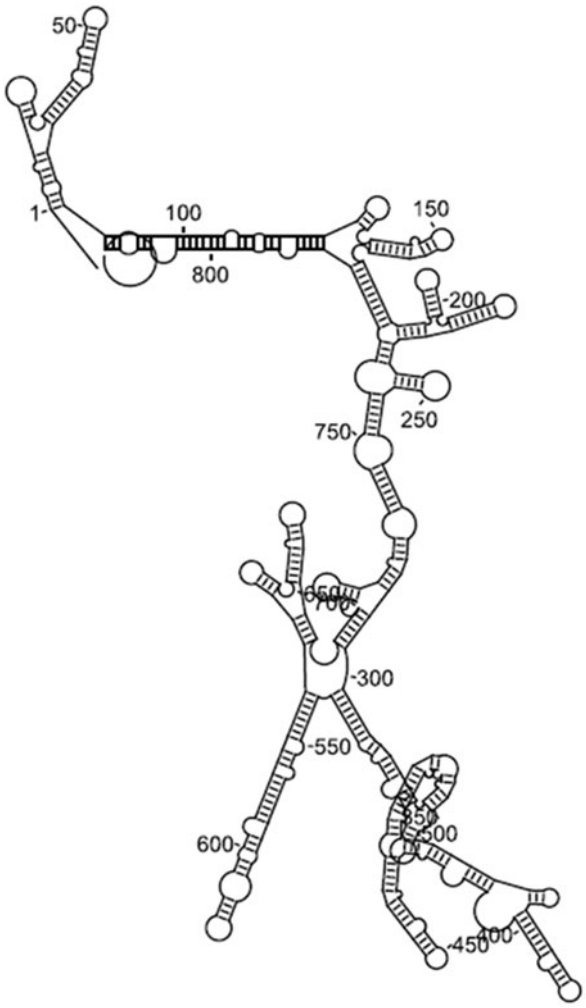

Fig. 10.1 BACE1-AS secondary structure. The correlation of lncRNAs to Alzheimer's disease is already presented in several latest studies modulating Aβ formation or impacting apoptosis and affecting Alzheimer's disease development or progression (Fukumoto et al. 2002; Mus et al. 2007; Parenti et al. 2007; Faghihi et al. 2008a, b, 2010; Modarresi et al. 2011; Ng et al. 2013; Luo and Chen 2016; Kim et al. 2016). (Adapted form Ashraf et al. 2019. This is an Open Access article which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. This is distributed under the terms of the Creative Commons Attribution License)

and Mathews 2012; Janssen and Giegerich 2014; Xu and Chen 2015; Sloma and Mathews 2017; Jabbari et al. 2018; Ashraf et al. 2019). In a latest study, the DMfold method has been presented to predict RNA secondary structures with pseudoknots based on the deep learning technique and the improved base pair maximization principle (Wang et al. 2019). Additionally, researchers demonstrated the IRIS method (Python-based) for predicting RNA secondary structures based on PARIS (Psoralen Analysis of RNA Interactions and Structures) data (Zhou et al. 2020).

By taking into consideration the latest presentation of the AlphaFold artificial intelligence system for the prediction of a protein 3d structure using the DeepMind platform (Senior et al. 2019, 2020), most of the RNA M-folding algorithms concentrate on the RNA secondary structure. Many computational methods are already published for the prediction of RNA secondary structure (Fig. 10.1) either based on

thermodynamic models that calculate the free energy or using the homologous RNA sequences, such as the free energy-based algorithms, the free energy minimization algorithm, the Sfold algorithm, the expected accuracy maximization algorithm, or the structure profiling experiments (Mathews and Turner 2002; Hofacker 2003; Knudsen and Hein 2003; Zuker 2003; Underwood et al. 2010; Hajiaghayi et al. 2012; Puton et al. 2013; Hamada 2015a, b; Lorenz et al. 2016; Yan et al. 2016; Smola and Weeks 2018; Saus et al. 2018; Yu et al. 2020).

10.2 RNA Secondary Structure: Formalism and Representation

Let us recall the basic definition of secondary structures (Ashraf et al. 2019). A secondary structure S on a sequence s is the set of base pairs (s_i, s_j), where $i < j$ and where s_i represents the nucleotide at a position i on a sequence s that has the following properties:

(i) $$(s_i, s_j) \in S \Rightarrow (s_i, s_j) \in (AU, UA, GC, CG, GU, UG)$$

(ii) $$\big((s_i, s_j) \wedge (s_k, s_l)\big) \in S \wedge (s_i = s_k) \Rightarrow j = l$$

(iii) $$\big((s_i, s_j) \wedge (s_k, s_l)\big) \in S_i < k \Rightarrow l < j \vee j < k$$

Constraint (i) means that only Watson-Crick and wobble base pairs may form. Constraint (ii) states that a nucleotide may be involved in at most 1 base pair, and constraint (iii) implies that all base pairs are nested. While these constraints greatly simplify the folding algorithms, none of the above constraints is biologically relevant (Ashraf et al. 2019). Additionally, a few prediction solutions aim to predict secondary structures, including pseudoknots and non-nested pairs, simultaneously reducing the computational complexity like the programs ConStruct, HotKnots, ILM, NUPACK, PKNOTS, and RNA STAR (Eddy 2004; Schroeder 2009). In literature, RNA secondary structures can be displayed in different representations, including hairpin and interior loops, multi-loops, external loops, pseudoknots, and interior-pseudo-knotted loops (Fig. 10.2). Depending on the use, specific representations are more or less useful (Ashraf et al. 2019), such as the bracket notation, the trees, the arc-annotated sequences, the circles, the mountain plots for large RNAs, and the dot plots.

10.3 Mathematical Representations of Closed RNA Secondary Structures

A secondary structure of size n is closed if there is an h-bond connecting base 1 and n (Doslic and Veljan 2007). For given integers $n \geq 2$, $l \geq 0$, there are $S^{(l)}(n-2)$ secondary structures of size n and rank l, also establishing a bijection between the set of all closed secondary structures $z^{(l)}(n)$ and the set of all plane trees with exactly

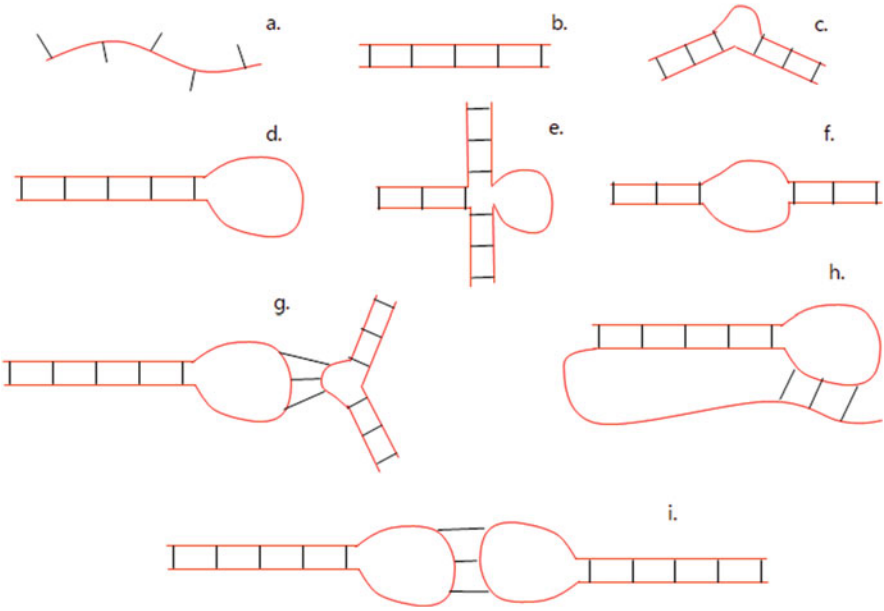

Fig. 10.2 RNA secondary structures elements, predictable by identifying the structure that minimizes the free energy of the folded molecule (Adapted from clcbio Main Workbench educational presentations): (**a**) single-stranded RNA, (**b**) double-stranded RNA helix of stacked based pairs, (**c**) bulge loop, (**d**) stem and loop or hairpin loop, (**e**) junctions or multi-loops, (**f**) interior loop, (**g**) hairpin bulge, (**h**) pseudoknots, (**i**) kissing hairpins

n leaves $T^{(l)}(n)$ (Ashraf et al. 2019). Base pairs like C-G, A-U, and G-U form h-bonds, which cause folding of the molecular backbone into a configuration of minimal energy (Doslic and Veljan 2007; Ashraf et al. 2019).

An alternative definition of closed secondary structures has been given (Rastegari and Condon 2005), through the closed regions of a secondary structure: representing a secondary structure as an arc diagram, in which base indices are shown as vertices on a straight line, ordered from the 5′-end and arcs, indicate base pairs, a region $[i; j]$ will be referred to as weakly closed if it contains at least one base pair and for all base pairs $i' \cdot j'$ of R, $i' \in [i; j]$ if and only if $j' \in [i; j]$ and closed if either $i = 1, j = n$ or if it is weakly closed and for all l with $i < 1 < j$ the regions $[i; 1]$ and $[1; j]$ are not weakly closed.

10.3.1 Closed RNA Representation as a *k*-Non-crossing Set of Partitions

Geometrically, a closed k-non-crossing RNA secondary structure can be represented either as a simple, closed curve or as a system of k such curves as it is already published through the genetic algorithm RnaPredict (Deschenes 2005) and the

parallelized version of this algorithm P-RnaPredict (Hendriks 2005). Besides, Zhan and Guo (2005) proposed a permutation-based genetic algorithm using the Standard Roulette Wheel Selection (STDS) and the KBR strategy. According to these authors, a closed RNA secondary structure is represented as a k-non-crossing set of partitions representing the base and no base pairs, respectively. It should be noted at this point that the combinatorial properties of secondary structures are derived from Waterman's recursion (Waterman 1987) as follows:

$$S_2(n) = S_2(n-1) + \sum_{S=0}^{n-2} S_2(n-2-s)S_2(s),$$

where $S_2(n)$ denotes the number of RNA secondary structures.

Even though the above genetic algorithms have already provided comparable results to the M-folding problem, the current benchmark for closed RNA secondary structure prediction, unfortunately, they have polynomial-time solutions.

10.3.2 Closed RNA Representation as Motzkin Words and Paths

Arc-annotated sequences represent RNA molecules' structural information and have been extensively used for the RNA secondary prediction. As we mentioned before, an arc-annotated sequence is a sequence over a given alphabet together with additional structural information specified by arcs connecting pairs of positions. The arcs determine the way the sequence folds into a three-dimensional space. Arc-annotated sequences can be classified according to the combinatorial structure of their arcs.

Stein and Waterman (1978) proved that the sequences arising in the enumeration of secondary structures that can occur under various reasonable restrictions might be considered as natural generalizations of the Catalan and Motzkin numbers (A001006) (Sloane n.d.). To define the Motzkin word, we recall an equivalent definition for secondary structures introduced by Viennot and Vauchaussade de Chaumont (1985): For $x \in \Sigma$ denoting the number of occurrences of a symbol x in w. Then a word $w \in \Sigma^n$ is a secondary structure of size n if w it satisfies the three following conditions:

1. For every factorization $w = u \cdot v$, $|u|_{(\geq |u|)}$.
2. $|w|_{(=|w|)}$.
3. w has no factor ().

Within this notation, a pair of corresponding brackets within a word w represents two single-stranded nucleic acid bases, which are paired. The symbol | represents an unpaired base. The words Σ^*, which satisfy conditions (1) and (2) of the previous definition, are called Motzkin words. Condition (3) accommodates that a hydrogen bond cannot link together two adjacent bases. Consequently, loops consist of at least

one base within our model, while a realistic assumption would force the loops to consist of at least three bases. Note that Motzkin words abstract from the fact that RNA contains four different nucleotides. Any Motzkin word of length n represents 4^n pairwise different RNA structures. Loads are impossible because of pairing constraints, but this matter is handled in the same manner as impossible loop or stem lengths. As long as all concerned models abstract in the same way, the results obtained on Motzkin words can be transferred to closed RNA secondary structures.

A Motzkin path is a lattice path in the first quadrant beginning at the origin, ending at the x-axis and consisting of the steps $u = (1,1)$ as the up-step, $d = (1,-1)$ as the down-step, and $h = (1,0)$ as the horizontal step. The set of all Motzkin paths of length n has been already enumerated by the n-th Motzkin number $M_n = \sum_{k\geq 0} \binom{n}{2k} C_k$ (Donaghey and Shapiro 1977). It has also been proved that secondary structures are in a simple bijection with Motzkin paths without peaks (Deutsch and Shapiro 2002).

In the general case of the RNA-RNA Interaction Prediction Problem (Tsiamis et al. 2016), it is assumed that there exist two independent RNA sequences K and L of length n and m, respectively. In a specific joint secondary structure of K and L, each nucleotide is paired with at most one nucleotide in the same or the other strand, while these two strands interact in opposite directions. If we assume that the K strand is indexed from 1 to n in $5'$ to $3'$ direction and L is indexed from 1 to m in $3'$ to $5'$ direction, then we refer to the ith nucleotide in K and L by i_K and i_L, respectively, and to any base pair between nucleotides i and j with the notion $i \cdot j$.

There are several methods in the literature for the prediction of a joint structure formed by two interacting RNAs: base pair counting, grammar-based approach to RNA-RNA interaction prediction, stacked pair energy model or loop energy model (Alkan et al. 2006), and RNA interaction structures combinatorics like generating functions, singularity analysis, as well as recurrence relations and asymptotic formulas for the number of joint structures (Li et al. 2008, 2011).

10.4 RNA Secondary Structures in Neurodegeneration

Several research studies focus on the role of specific proteins in neurodegenerative disorders like Alzheimer's disease (AD) and autism spectrum disorders (Alexiou et al. 2018a, b, c, 2019). In a latest study, a computational analysis of lncRNAs and their potential correlation to AD pathologies and lesions have been presented, including the secondary structures of four proteins related to Alzheimer's disease, BACE1, Rad18, GABABR2, and hnRNPQ, targeted from the corresponding lnRNAs BACE1-AS, NAT-Rad18, 17A, and hnRNP Q (Ashraf et al. 2019). In this chapter, we present the secondary structure prediction table (**Appendix**), using the same computational tool (QIAGEN CLC Main Workbench 8.0; QIAGEN CLC Main Workbench Software n.d.) and the identical sequences imported from the

Protein Databank, 6EJ3(BACE1_HUMAN), 4F12(GABABR2_HUMAN), 4UX8 (hnRNPQ_HUMAN), and 2Y43(RAD18_HUMAN).

10.4.1 How Can Pathogenic RNA Structures Cause Neurodegenerative Disease?

Several of the functional secondary structural elements can suddenly appear as pathogenic agents due to point mutations, sequence deletions, and expansions. The newly formed mutated RNA motifs can interfere with normal interaction and initiate the cells' pathologic processes. Some of the widely acknowledged instances of such gain of function comprise dysregulation of site-specific RNA editing by adenosine deaminase acting on RNA (ADAR), sequestration of RNA-binding proteins, the formation of pseudo internal ribosome entry sites (IRES), activation of cryptic splicing sites, and subsequent cap-independent translation, i.e., repeat-associated non-ATG (RAN) translation (Mirkin 2007; Zu et al. 2011). The formation of several peptides in the absence of canonical AUG start codons has been exhibited through broad-scale proteomics and transcriptome studies (Lee et al. 2012; Stern-Ginossar et al. 2012; Slavoff et al. 2013). Hence, the biological implications of understanding RAN translation are not just restricted to pathologic RNA structures.

Pathogenic RNA folding is attributable to various factors. The functional role played by a specific RNA structural motif is revealed by disease pathogenesis. A common cause of abnormal RNA folding is single nucleotide polymorphisms (SNP). The conformational stability of a secondary structure element can change a single nucleobase mutation. This can lead to a downstream pathology and disrupt a fragile equilibrium of RNA-protein interaction networks. MAPT (Tau) mRNA, vide infra being one of the intensely studied instances (Warf and Berglund 2010).

Activation of cryptic splicing sites contributes to the diversity of protein isoform when pre-mRNAs intronic regions undergo retrotransposon insertions. An important role is played by this mechanism in brain development, evolution, and cellular differentiation. However, in most instances, it is also a contributing factor to genetic diseases (Deininger and Batzer 1999; Baillie et al. 2011). For instance, an essential role in the assembly of signal recognition particles (SRPs) is played by the structured retrotransposon Alu element of 7SL RNA. In the human genome, the Alu motif is the most abundant retrotransposon. With more than a million copies, the Alu motif represents almost 11% of the entire genome (Lander et al. 2001). Cryptic exons can be activated when the intronic region's insertion of Alu elements occurs, thereby leading to unnatural protein isoforms being formed (Vervoort et al. 1998; Pagani and Baralle 2004). Large gene fragments deletion can also result from the Alu element-driven abnormal recombination, and propagation of linked pathology is caused by co-migration of the other pathologic RNA fragments (Nakayama et al. 2010; Iida et al. 2012).

In the case of microsatellite repeat expansion disorders, strand slipping during replication, repair, and recombination results from particular DNA oligonucleotide fragments (repeated sequences) that fold into stable hairpins. As a result, there is the

formation and elongation of such repetitive fragments (Gacy et al. 1995; López Castel et al. 2010). The corresponding single-stranded RNA comprises the expanded repeated sequence formed due to transcription. As a result of the presence of additional secondary structural elements, this repeated sequence is folded aberrantly. A high likelihood of expanded repeats is folded in abnormal structures once their stable incorporation in the DNA sequence occurs. This subsequently leads to a gradual augmentation of the pathology with age, and in future generations, it manifests in the form of a phenomenon recognized as repeat instability (Kovtun and McMurray 2008; Liu et al. 2010; López Castel et al. 2010).

10.4.2 lncRNAs and Alzheimer's Disease

Mammalian genomes encode tens of thousands of lncRNAs, and up to 40% of these lncRNAs are explicitly expressed in the brain (Briggs et al. 2015). Several neurodegenerative ailments have been attributed to abnormal lncRNA expression. Significantly, the differential expression of hundreds of lncRNAs has been reported in 3xTg-AD model mice compared to the age-matched control animals. Additionally, in comparison to control animals, 150 lncRNAs are found to be upregulated, and 99 lncRNAs are observed to be downregulated in the hippocampus of APP/PS1 transgenic mice. When transcriptome analyses were conducted on postmortem human brains, it was identified that in the AD patient brains, levels of multiple lncRNAs had been altered substantially. Together, in animal models and AD patients, the differential expression of lncRNAs takes place. Thus, lncRNAs can serve as biomarkers and probable treatment targets for AD (Li et al. 2020). Based on the size, non-coding RNAs (ncRNAs) can be categorized into IncRNAs and short RNAs (<200 nt in length) (Modarresi et al. 2011; Magistri et al. 2012). Lacking an apparent open reading frame, IncRNAs vary in size from 200 nt to more than 100 kb (Derrien et al. 2012; Harrow et al. 2012; Knauss and Sun 2013; Zhu et al. 2013). IncRNAs associated with particular functions are conserved evolutionarily (Hamada 2015a, b; Iwakiri et al. 2016). They localize at particular types of cells and subcellular compartments and regulate dynamically (Knauss and Sun 2013; Washietl et al. 2014; Wilk et al. 2016). At various levels, gene expression is regulated by IncRNAs (Melissari and Grote 2016). In line with epigenetic regulations' primary function, the bulk of the IncRNAs are present in the nucleus (Knauss and Sun 2013; Zeng et al. 2015). Though IncRNAs are not regarded as a "dark matter" instead, they have extremely important roles for controlling the translation and transcription along with, during chromatin modification regulation of the cell cycle, genome rearrangement, genetic imprinting, messenger RNA (mRNA) decay, splicing, transcription, and translation (Derrien et al. 2011; Zhu et al. 2013; Iwakiri et al. 2016). Investigations into the genetic factors and pathomechanism of AD have been ongoing for over a century. While the research continues, several studies have depicted that IncRNA dysregulation has a role to play in epilepsy, cancer, and neurodegenerative, cardiovascular, and genetic diseases. Some studies have also indicated that IncRNAs also have a substantial role in AD (Kraus et al. 2015; Sun et al. 2016; Melissari and Grote

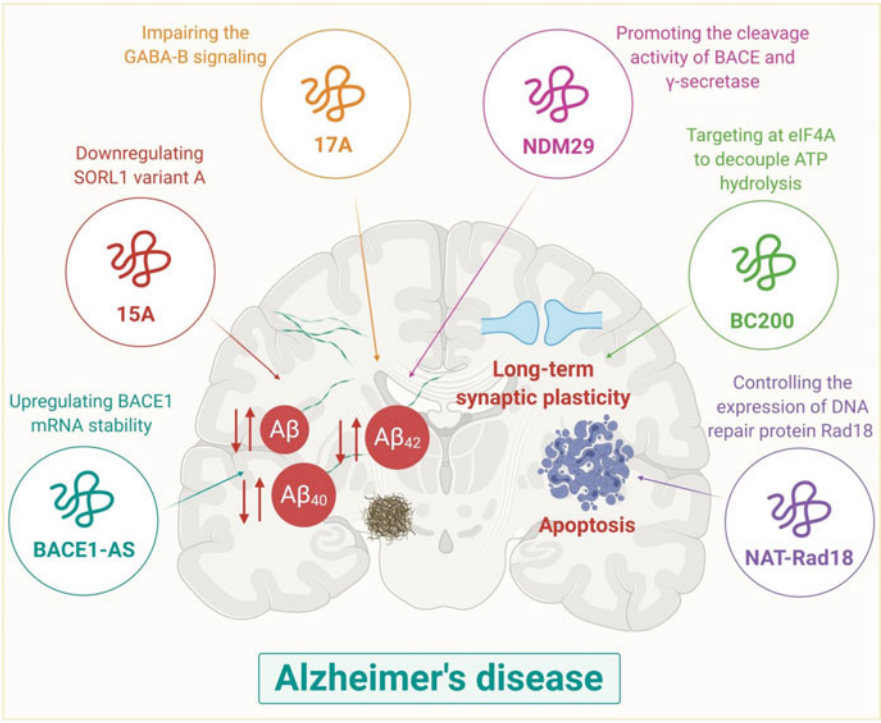

Fig. 10.3 Schematic diagram showing dysregulated lncRNAs in AD. BACE1-AS, 51A, 17A, and NDM29 directly/indirectly enhance Aβ formation and/or the Aβx-42/Aβx-40 ratio. To maintain long-term synaptic plasticity, BC200 regulates local protein synthesis. NAT-Rad18 has a major role in apoptosis. Abbreviations: Aβ, amyloid β peptide; NDM29, neuroblastoma differentiation marker 29; BACE1, β-site AβPP cleaving enzyme-1; eIF4A, eukaryotic initiation factor 4A; BC200, brain cytoplasmic 200 RNA; SORL1, sortilin-related receptor gene; mRNA, messenger RNA

2016) (Fig. 10.3 and Table 10.1). Regardless of the role of IncRNAs in AD pathology, several factors such as hypoxia/ischemia (Jha et al. 2018), mitochondrial dysfunction (Jha et al. 2017a, b), impaired NF-κβ signaling (Jha et al. 2019a, b), altered IDE and NEP expression (Jha et al. 2015), ABC transporter dysfunction (Jha et al. 2019a, b), altered ion channels (Kumar et al. 2016), and HIV infections (Jha et al. 2020) have also been reported to be associated with AD progression (Jha et al. 2017a, b; Kumar et al. 2015). Further, the linkage between various IncRNAs and AD has been discussed in succeeding sections.

10.4.3 BACE1-AS

β-site amyloid precursor protein cleaving enzyme-1 antisense transcript (BACE1-AS) is a well-conserved RNA transcribed from the positive strand of chromosome 11 on the parallel strand of the BACE1 locus (11q 23.3) (Faghihi et al. 2008a, b;

Table 10.1 The role of dysregulated lncRNAs and their associated target in Alzheimer's disease

lncRNAs	Target(s)	Function(s)	Reference(s)
51A	Downregulates SORL1 variant A	Aβ↑	Ciarlo et al. (2013), Ma et al. (2009)
BACE1-AS	Upregulates BACE1 mRNA stability	Aβ↑	Faghihi et al. (2008a, b)
17A	GABA B signaling impairment	Aβx-42/Aβx-40↑, Aβ↑	Massone et al. (2011), Gavazzo et al. (2013)
BC200	Decouples ATP hydrolysis via targeting at eIF4A	Acts as a regulator of local protein synthesis to maintain the long-term synaptic plasticity	Lin et al. (2008)
NAT-Rad18	Modulates Rad18 expression	Making the neuron more sensitive to apoptosis	Iacoangeli et al. (2010)
NDM29	Promotes BACE and γ-secretase activity	Aβx-42/Aβx-40↑, Aβ↑	Massone et al. (2012)

Modarresi et al. 2011). At the mRNA level as well as protein levels, regulation of BACE1 expression is performed by BACE1-AS. In toxic Aβ, a vital role is played by BACE1 (Mulder et al. 2010; Dash et al. 2014). In several varied cell stressors, the implication of AD pathogenesis has taken place. On exposure to increased temperature, staurosporine, serum starvation, Aβ1–42, high glucose, and both BACE1-AS and BACE1 mRNA are upregulated. This indicates that alteration of BACE1-AS expression and thereafter BACE1 enzyme activity can be caused by cell stressors (Faghihi et al. 2008a, b; Liu et al. 2014). Irrespective of whether BACE1-AS is overexpressed or knocked down, parallel regulation of BACE1 protein and BACE1 mRNA takes place, subsequently resulting in reduced Aβ production and plaque deposition (Faghihi et al. 2008a, b; Liu et al. 2014; Modarresi et al. 2011). In animals, several physiological and behavioral deficits result from loss of BACE1, including emotional deficits, memory loss, peripheral myelination defects, and reduced synaptic plasticity (Ma et al. 2007; Laird et al. 2005; Hu et al. 2006; Decourt and Sabbagh 2011; Borghi et al. 2007; Stockley and O'Neill 2008; Vassar and Kandalepas 2011). The complicated pathologic and physiologic boundaries indicate tighter regulation of the BACE1 expression (Vassar and Kandalepas 2011; Faghihi et al. 2008a, b). In summary, BACE1-AS levels are increased due to cell stress; this, in turn, results in simulation of the BACE1 expression, which has the potential of further enhancing AβPP processing and Aβ1–42 production. Overexpression of BACE1-AS can be further promoted through elevated Aβ1–42 levels along with the AβPP processing cascade in a feedforward manner (Faghihi et al. 2008a, b; Liu et al. 2014; Dislich and Lichtenthaler 2012). BACE1-AS increases the stability of the BACE1 mRNA through the formation of a RNA duplex (Yuan et al. 2013; Wan et al. 2017; Liu et al. 2014). Hence, both BACE1-AS and BACE1 can be potential biomarkers and treatment targets for AD (Evin and Hince 2013; Perneczky and Alexopoulos 2014; Dislich and Lichtenthaler 2012; Decourt and Sabbagh 2011).

10.4.4 51A

For a long time, it has been hypothesized that the neuronal sortilin-related receptor gene (SORL1, also known as SORLA and LR11) is involved in the pathogenesis of AD (Jacobsen et al. 1996; Yamazaki et al. 1997; Lee et al. 2008; Rogaeva et al. 2007). As per suggestions from recent studies, as a sorting receptor for AβPP holoprotein, SORL1 interacts with AβPP in endosomes and trans-Golgi networks, affecting trafficking and proteolytic processing (Ciarlo et al. 2013). Shifting of AβPP from the retromer recycling pathway to β-secretase cleavage pathway can be facilitated by the reduced SORL1 expression. This, in turn, results in Aβ formation due to increased secreted AβPP production (Ciarlo et al. 2013; Khvotchev and Sudhof 2004). 51A is a novel ncRNA that maps in an antisense configuration to intron 1 of the SORL1 gene, whose synthesis fosters the expression of SORL1 variants spliced alternatively. It must be noted that in the in vitro model and the AD brain, 51A is overexpressed. One probable mechanism through which 51A increases AD susceptibility is an increase in amyloid formation through downregulation of SORL1 variant A via alternative splicing (Ciarlo et al. 2013; Ma et al. 2009).

10.4.5 17A

17A is a 159-nt lncRNA that is synthesized by RNA polymerase III. 17A maps in intron 3 of G-protein-coupled receptor 51 gene (GPR51), endures alternative splicing, and increases the volume of GABA B2 receptor isoforms. Through activation of particular potassium channels and regulation of intracellular 3′–5′-cyclic adenosine monophosphate accumulation, GABA B's biological functions might be affected by GABA B R2 splice variant B. As a result of these events, GABA B signaling impairment increases Aβ secretion, and enhancement in the Aβx-42/Aβx-40 ratio occurs. When compared with control tissues, 17A RNA is upregulated in AD, indicating that there could be direct or indirect involvement with the AD mechanism (Massone et al. 2011; Gavazzo et al. 2013; Wan et al. 2017).

10.4.6 NDM29

Neuroblastoma differentiation marker 29 (NDM29) is an RNA polymerase III-transcribed ncRNA. NDM29 synthesis is induced by inflammatory stimulation in a dose-dependent manner. Altered AβPP modulation accompanies the upregulation of NDM29 RNA. In the meantime, it can also stimulate the BACE cleavage activities, resulting in the generation of an increased amount of AβPP C-terminal fragments. The fragments are meant for further processing by the γ-secretase cleavage complex increasing the Aβx-42/Aβx-40 ratio as well as the Aβ formation (Vella et al. 2015; Gavazzo et al. 2013; Massone et al. 2012).

10.4.7 BC200

Brain cytoplasmic 200 RNA (BC200) is a translational regulator that targets eukaryotic initiation factor 4A. It, in turn, assists with modulating local protein synthesis in postsynaptic dendritic microdomains, decoupling adenosine triphosphate hydrolysis from RNA duplex unwinding, and contributing to the maintenance of long-term synaptic plasticity (Lin et al. 2008). As per a postmortem study, there is a reduction of 60% in the BC200 RNA levels in cortical areas in individuals between the age of 49 and 86 years. There is a substantial upregulation in a BC200 RNA in an AD brain compared with a normal brain that has been age-matched. Along with an increase in disease progression, the comparative BC200 RNA levels increase in AD-involved brain areas. Still, BC200 downregulation was reported by at least one study (Mus et al. 2007). The contradiction between the studies can be attributed to the varying severity of the disease and variations in the brain regions, but atypical BC200 RNA expression is a distinct possibility (Wu et al. 2013). In somata, the comparative BC200 RNA levels increase, while they decrease in dendrites. As a result of this varying expression, there is an effect on microtubule-dependent transport, subsequently contributing to dendritic and axonal blockage, indicating early events in AD. Subsequently, it can contribute to local Aβ generation, followed by amyloid deposition (Iacoangeli et al. 2010; Zhou and Xu 2015). Findings from another group indicate that there is no effect on BC200 RNA under apoptotic conditions in vitro. The findings also hypothesized that BC200 is involved in necrosis instead of apoptosis (Liu et al. 2015).

10.4.8 NAT-Rad18

One of the primary forms of programmed death of a cell is apoptosis. Progressive cell loss resulting from excessive apoptosis contributes to various neurodegenerative ailments, including AD. Rad18 is a member of the Rad6 epistasis group that handles the responsibility for post-replication repair. By encoding a spectrum of DNA-damaging agents, NAT-Rad18 genes encode for natural antisense transcripts against Rad18. In the protein and mRNA levels, the relationship between NAT-Rad18 and Rad18 is Rad18 showcases counter-balanced, wherein low expression level. Following exposure to Aβ, there is a differentially upregulated expression of NAT-Rad18 in the brain tissues, especially the cortical neurons. When considered in its entirety, there are indications from this evidence that through its effects on the DNA repair system, AD may have involvement of NAT-Rad18 (Parenti et al. 2007). Further, the summary of all these IncRNAs and their target with respect to AD has been addressed in Table 10.1.

10.5 Conclusion

This chapter has comprehensively addressed the representation, visualization, and mathematical formulation of RNA secondary structures, which can be viewed as steps toward the three-dimensional prediction modeling and their role in neurodegeneration, especially in AD. Almost all AD-related lncRNAs have been listed in this chapter, but the investigation into this field is very early. We still need to elucidate how lncRNAs operate at the molecular and cellular levels as the lncRNA field continues to develop. Most recent studies advocate that lncRNAs are potential candidates in the ongoing quest for AD biomarkers and could facilitate identification of rational therapeutic strategies. A deep understanding of lncRNA biology could unlock more avenues to early AD diagnosis and treatment.

Appendix: Secondary Structure Prediction

Sequence	Start	End	Region name
UBE2A_HUMAN	4	16	Alpha helix
UBE2A_HUMAN	33	41	Beta strand
UBE2A_HUMAN	53	59	Beta strand
UBE2A_HUMAN	70	74	Beta strand
UBE2A_HUMAN	82	82	Beta strand
UBE2A_HUMAN	87	88	Beta strand
UBE2A_HUMAN	89	93	Alpha helix
UBE2A_HUMAN	102	112	Alpha helix
UBE2A_HUMAN	124	148	Alpha helix
RAD18_HUMAN	4	6	Alpha helix
RAD18_HUMAN	13	24	Alpha helix
RAD18_HUMAN	27	38	Beta strand
RAD18_HUMAN	48	55	Alpha helix
RAD18_HUMAN	63	67	Beta strand
RAD18_HUMAN	75	97	Alpha helix
RAD18_HUMAN	113	117	Beta strand
RAD18_HUMAN	123	128	Alpha helix
RAD18_HUMAN	130	141	Alpha helix
RAD18_HUMAN	146	152	Alpha helix
RAD18_HUMAN	160	162	Alpha helix
RAD18_HUMAN	166	168	Alpha helix
RAD18_HUMAN	175	178	Alpha helix
RAD18_HUMAN	183	185	Alpha helix
RAD18_HUMAN	196	200	Alpha helix
RAD18_HUMAN	214	223	Alpha helix
RAD18_HUMAN	226	238	Alpha helix
RAD18_HUMAN	246	250	Alpha helix

(continued)

Sequence	Start	End	Region name
RAD18_HUMAN	253	263	Alpha helix
RAD18_HUMAN	271	291	Alpha helix
RAD18_HUMAN	295	318	Alpha helix
RAD18_HUMAN	322	324	Alpha helix
RAD18_HUMAN	325	326	Beta strand
RAD18_HUMAN	332	365	Alpha helix
RAD18_HUMAN	372	374	Beta strand
RAD18_HUMAN	381	387	Alpha helix
RAD18_HUMAN	410	413	Alpha helix
RAD18_HUMAN	425	432	Alpha helix
RAD18_HUMAN	444	460	Alpha helix
RAD18_HUMAN	473	485	Alpha helix
HNRPQ_HUMAN	19	22	Alpha helix
HNRPQ_HUMAN	27	33	Alpha helix
HNRPQ_HUMAN	36	54	Alpha helix
HNRPQ_HUMAN	58	68	Alpha helix
HNRPQ_HUMAN	70	80	Alpha helix
HNRPQ_HUMAN	85	89	Alpha helix
HNRPQ_HUMAN	91	106	Alpha helix
HNRPQ_HUMAN	112	112	Beta strand
HNRPQ_HUMAN	121	130	Alpha helix
HNRPQ_HUMAN	135	135	Beta strand
HNRPQ_HUMAN	137	137	Beta strand
HNRPQ_HUMAN	163	166	Beta strand
HNRPQ_HUMAN	171	184	Alpha helix
HNRPQ_HUMAN	191	193	Alpha helix
HNRPQ_HUMAN	205	210	Beta strand
HNRPQ_HUMAN	213	223	Alpha helix
HNRPQ_HUMAN	234	240	Beta strand
HNRPQ_HUMAN	245	247	Beta strand
HNRPQ_HUMAN	256	273	Alpha helix
HNRPQ_HUMAN	274	276	Beta strand
HNRPQ_HUMAN	288	292	Beta strand
HNRPQ_HUMAN	297	307	Alpha helix
HNRPQ_HUMAN	311	314	Beta strand
HNRPQ_HUMAN	320	322	Beta strand
HNRPQ_HUMAN	331	375	Alpha helix
HNRPQ_HUMAN	382	391	Alpha helix
HNRPQ_HUMAN	401	405	Beta strand
HNRPQ_HUMAN	412	432	Alpha helix
HNRPQ_HUMAN	611	617	Alpha helix
GDNF_HUMAN	4	15	Beta strand
GDNF_HUMAN	59	76	Alpha helix
GDNF_HUMAN	81	85	Alpha helix

(continued)

Sequence	Start	End	Region name
GDNF_HUMAN	89	91	Alpha helix
GDNF_HUMAN	93	97	Alpha helix
GDNF_HUMAN	118	127	Beta strand
GDNF_HUMAN	137	143	Alpha helix
GDNF_HUMAN	144	144	Beta strand
GDNF_HUMAN	150	164	Alpha helix
GDNF_HUMAN	167	170	Alpha helix
GDNF_HUMAN	188	190	Alpha helix
GDNF_HUMAN	193	202	Alpha helix
GABR2_HUMAN	21	32	Alpha helix
GABR2_HUMAN	66	70	Alpha helix
GABR2_HUMAN	78	94	Alpha helix
GABR2_HUMAN	96	103	Alpha helix
GABR2_HUMAN	111	122	Alpha helix
GABR2_HUMAN	128	131	Beta strand
GABR2_HUMAN	139	146	Alpha helix
GABR2_HUMAN	151	156	Beta strand
GABR2_HUMAN	171	175	Beta strand
GABR2_HUMAN	184	198	Alpha helix
GABR2_HUMAN	200	216	Alpha helix
GABR2_HUMAN	218	219	Beta strand
GABR2_HUMAN	224	226	Beta strand
GABR2_HUMAN	240	243	Alpha helix
GABR2_HUMAN	248	252	Beta strand
GABR2_HUMAN	257	265	Alpha helix
GABR2_HUMAN	268	270	Alpha helix
GABR2_HUMAN	277	281	Beta strand
GABR2_HUMAN	289	296	Alpha helix
GABR2_HUMAN	300	312	Alpha helix
GABR2_HUMAN	325	329	Alpha helix
GABR2_HUMAN	335	342	Alpha helix
GABR2_HUMAN	362	378	Alpha helix
GABR2_HUMAN	382	386	Alpha helix
GABR2_HUMAN	396	402	Alpha helix
GABR2_HUMAN	411	411	Beta strand
GABR2_HUMAN	414	418	Beta strand
GABR2_HUMAN	426	429	Beta strand
GABR2_HUMAN	437	438	Beta strand
GABR2_HUMAN	442	458	Alpha helix
GABR2_HUMAN	467	478	Alpha helix
GABR2_HUMAN	481	498	Alpha helix
GABR2_HUMAN	499	502	Beta strand
GABR2_HUMAN	510	513	Alpha helix
GABR2_HUMAN	522	525	Beta strand

(continued)

Sequence	Start	End	Region name
GABR2_HUMAN	529	537	Beta strand
GABR2_HUMAN	543	544	Beta strand
GABR2_HUMAN	549	566	Beta strand
GABR2_HUMAN	571	572	Beta strand
GABR2_HUMAN	575	583	Beta strand
GABR2_HUMAN	590	592	Beta strand
GABR2_HUMAN	596	601	Beta strand
GABR2_HUMAN	604	618	Beta strand
GABR2_HUMAN	624	627	Beta strand
GABR2_HUMAN	639	641	Beta strand
GABR2_HUMAN	653	664	Beta strand
GABR2_HUMAN	666	677	Beta strand
GABR2_HUMAN	681	682	Beta strand
GABR2_HUMAN	691	692	Beta strand
GABR2_HUMAN	694	713	Beta strand
GABR2_HUMAN	719	741	Beta strand
GABR2_HUMAN	743	748	Beta strand
GABR2_HUMAN	753	755	Alpha helix
GABR2_HUMAN	760	761	Beta strand
GABR2_HUMAN	777	777	Beta strand
GABR2_HUMAN	786	794	Alpha helix
GABR2_HUMAN	796	816	Alpha helix
GABR2_HUMAN	824	828	Alpha helix
GABR2_HUMAN	831	840	Alpha helix
GABR2_HUMAN	851	856	Alpha helix
GABR2_HUMAN	885	895	Alpha helix
GABR2_HUMAN	898	901	Alpha helix
GABR2_HUMAN	935	938	Beta strand
BACE1_HUMAN	7	9	Alpha helix
BACE1_HUMAN	10	11	Beta strand
BACE1_HUMAN	26	27	Beta strand
BACE1_HUMAN	60	64	Beta strand
BACE1_HUMAN	75	81	Beta strand
BACE1_HUMAN	88	92	Beta strand
BACE1_HUMAN	109	118	Alpha helix
BACE1_HUMAN	120	124	Alpha helix
BACE1_HUMAN	128	130	Beta strand
BACE1_HUMAN	145	147	Beta strand
BACE1_HUMAN	154	158	Beta strand
BACE1_HUMAN	160	163	Beta strand
BACE1_HUMAN	169	171	Beta strand
BACE1_HUMAN	177	186	Alpha helix
BACE1_HUMAN	187	187	Beta strand
BACE1_HUMAN	201	203	Alpha helix

(continued)

Sequence	Start	End	Region name
BACE1_HUMAN	213	215	Beta strand
BACE1_HUMAN	226	229	Beta strand
BACE1_HUMAN	235	237	Beta strand
BACE1_HUMAN	244	245	Beta strand
BACE1_HUMAN	249	251	Beta strand
BACE1_HUMAN	256	269	Beta strand
BACE1_HUMAN	287	288	Beta strand
BACE1_HUMAN	299	312	Alpha helix
BACE1_HUMAN	323	323	Beta strand
BACE1_HUMAN	327	332	Beta strand
BACE1_HUMAN	340	341	Beta strand
BACE1_HUMAN	343	348	Beta strand
BACE1_HUMAN	351	352	Beta strand
BACE1_HUMAN	357	361	Beta strand
BACE1_HUMAN	366	366	Beta strand
BACE1_HUMAN	373	373	Beta strand
BACE1_HUMAN	382	385	Beta strand
BACE1_HUMAN	393	400	Beta strand
BACE1_HUMAN	402	406	Beta strand
BACE1_HUMAN	412	422	Beta strand
BACE1_HUMAN	427	429	Alpha helix
BACE1_HUMAN	435	438	Beta strand
BACE1_HUMAN	452	469	Alpha helix
BACE1_HUMAN	474	478	Beta strand
BACE1_HUMAN	479	499	Alpha helix

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Immunotherapy: An Approach to Treat Alzheimer's Disease and Autism Spectrum Disorder

11

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Abstract

Since the late 1980s, Alzheimer's disease (AD) and autism spectrum disorder (ASD) had spread rapidly, and still, it persists in growing numbers. According to recent statistics, around 50 million people globally live with AD, and 1 out of 54 children have ASD, reaching an epidemic scale. Both diseases are thought to be the resultant of the build-up of abnormal proteins plaque/fibrils in the brain; the major cause of the difference is age. Though several kinds of research have been made, the detailed understanding of the mechanism behind the disease etiology, progression, early diagnosis, and other genetic factors is yet to be explored. In the past few years, only a few Alzheimer's patients were given proper medication using current drug therapeutics. Still, it gave only short relief and reverted in one form or the other, probably due to unblocked cognitive decline progression. For decades, the development of potential therapies for AD and ASD pathogenesis revolves around the aggregated proteins in neurodegenerative diseases. The emerging and expanding field of immunotherapy directs the clearing of these proteins which are responsible for cognitive impairment. Here, particular emphasis will be placed on the current immune therapeutics that have reached clinical trials. We also intend to divulge the connection between AD and ASD by

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deciphering the connecting mechanisms involved in the aggregated/toxic proteins, such as amyloid-β peptide (Aβ), Aβ precursor protein (APP), tau, α-synuclein, and apolipoproteins.

Keywords

Immunotherapy · Alzheimer's · Autism · Amyloid-β peptide (Aβ) · Aβ precursor protein (APP) · Apolipoproteins

Abbreviations

AD	Alzheimer's disease
APOE	Apolipoprotein E
APP	Amyloid precursor protein
ASD	Autism spectrum disorder
CAA	Cerebral amyloid angiopathy
ChAT	Acetylcholinesterase
CNTNAP2	Contactin-associated protein-like 2
DLBs	Lewy bodies
FHR1	Complement factor H-related protein
FN1	Fibronectin 1
IL	Interleukins
LPO	Lipid peroxidation
ROS	Reactive oxygen species
BBB	Blood-brain barrier

11.1 Introduction

Autism spectrum disorder (ASD) and Alzheimer's disease (AD) are two clinical syndromes that are distinct and uncommon by the concept; however, some similarities are apparent. Both AD and ASD are neurodegenerative and neurodevelopmental complex disorders, respectively, involve brain development primarily, and are also quite often associated with abnormalities of immune responses with devastating effects not only on the individual but also on society (Khan et al. 2016). AD, like many other acute and chronic neurodegenerative diseases, is associated with local inflammation clinically manifested by progressive dementia (Moya-Alvarado et al. 2016). AD's pathological characteristics are deposition of distinctive extracellular plaques of amyloid-b and tau neurofibrillary tangles associated with cognitive and mental dysfunction and cerebral amyloid angiopathy (CAA) in arterial walls (Serrano-pozo et al. 2011). On the other hand, ASD is characterized by social communication or interaction and restricted and repetitive behaviors. One of the studies of autism disease stated that autism and cancer share

several similarities at the level of cellular and molecular signal transduction, the involvement of the immune system, and the microbiota. Lymph stagnation in the brain may lead to neuroinflammation that is responsible for autism symptoms (Antonucci et al. 2019). Disease-related genes and their products make the background of common associations like memory deficits, demyelination, cognition changes, oxidative stress, and inflammation, as an integral part of both AD and ASD (Khan et al. 2016).

The systemic administration of steroidal or nonsteroidal anti-inflammatory drug treatments also failed to affect disease progression, leaving the scientific community with the question of what had been missed in understanding the disease (Schwartz et al. 2020).

More recently, it was found that brain-immune crosstalk is impaired in aging and neurodegenerative diseases. Thus, a fundamental mechanism of maintenance and support might be lost that could be amenable to restoration by rejuvenating the immune system (Scheiblich et al. 2020).

It would not be surprising enough that clinical immunotherapeutic approaches for other manifestations like cancer might be a suitable and fruitful therapy in the field of AD and ASD. By the use of clinical immunotherapeutic approaches in empowering the peripheral immune system, it might be possible to overcome the difficulties of co-ordinately targeting multiple factors that contribute to disease escalation and cognitive impairment, which may differ between patients, and at different phases along with the course of the disease (Alsharoqi et al. 2020). Therefore, in general, immunotherapy could serve as a means to harness the immune system to fight diseases like AD and ASD.

11.2 Common AD and ASD Manifestations

11.2.1 Common Recognizable Symptoms of AD and ASD

Significant fall in motor skills thought and behavioral coordination, apraxia, significant fall of expected chronological age with stereotyped repetitive movements including body shaking and clapping, inability to position parts of the body in space, and problems in changing clothes are the major characteristic features of ASD. All this can result in loss of independence as manifested by the incapability to perform routine jobs of performing daily ablutions, washing, dressing up, cooking, and eating. In case of AD progression from the mild to the moderate stages, alterations of the motor cortex, over-excitation, language problem, difficulties in judgment, unseemly behavior, disinhibition, difficulties to troubleshoot task persistence, restriction to verbal memory, alterations with the gamma-aminobutyric acid, and cholinergic pathways and impairments in the frontal lobe were reported (Nagata et al. 2010). Language circumlocution, dysfluent aphasia, difficulties in spontaneous speech, and frequent tip-of-the-tongue experiences are common symptoms of the two diseases. Early-stage symptoms specifically include dysfunctions in the non-linguistic areas of attention and executive memory. Simultaneously, stereotyped

communication is observed only on the progression of the disease; lowered semantic vocabulary, hindered search activities, poor language scores, and the progression in language impairment have been shown to correlate with clinical progression of AD. AD patients' facial recognition defects are due to their semantic nature. Moreover, patients of AD and ASD found difficulties in naming the person in question than in recognition and perception. These deficits affect most individuals and may vary from benign problems to more severe cognitive changes; nevertheless, the deficits were more pronounced when patients were imposed with demanding tasks (Hodges et al. 1993).

11.2.2 Genetics Association and Pathogenesis of AD and ASD

Numerous genes are highly active during nervous system development and are critical for the proper formation of any impairment that leads to ASD and AD pathogenesis (Blaker-Lee et al. 2012). ASD is a multigenic and highly heterogeneous group of disease that often coexist with other comorbidities caused by both inheritable and de novo gene variations. To distinguish which genes truly have overlapping risk is a considerable task to discuss common phenotypes. Generally, proteins responsible for energy metabolism, myelination, and synaptic vesicle are reported to be dysregulated in the brain of ASD patients. Apolipoprotein (apo) B-100, complement factor H-related protein (FHR1), complement C1q, and fibronectin 1 (FN1) are the common dysregulated proteins reported in the serum of individuals with ASD (Pichitpunpong et al. 2019). The most causative genes that lead to AD pathogenesis are β- amyloid, amyloid-β (Aβ)-mediated plaque formation, different conformations of Aβ, amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2) genes, and α-synuclein (Alzheimer's Association 2021).

α-synuclein association with many neurodegenerative diseases is collectively termed as synucleinopathies. These disorders include cognitive impairment, AD, ASD, PD, and dementia with Lewy bodies (DLBs). Misfolding and overexpression of α-synuclein lead to its aggregation and the formation of amyloid-like fibril in DLB region (Zhang et al. 2018).

α-synuclein via GSK3β (glycogen synthase kinase 3 beta) mediates phosphorylation of tau protein, leading to more Aβ production and accumulation, GSK3β activation, and intra-cellular dysfunctioning. Moreover, Aβ-associated α-synuclein aggregation in the limbic regions of AD patients facilitates more stable oligomers and hence disease pathogenesis (Crews et al. 2009; Twohig and Nielsen 2019).

The plethora of studies also reported the presence of α-synuclein in the CSF and plasma. α-synuclein plasma levels were found to be higher in ASD patients than in normal control. Besides, the involvement of α-synuclein in the regulation of synaptic plasticity leads to synaptic dysfunctioning, dopamine homeostasis imbalance, neurotransmitter disturbances, and sometimes neuronal death. Thus, these synucleinopathies and pathway disturbance might be strongly associated with ASD pathogenesis (Al-Mazidi and Al-Ayadhi 2021).

Other risk factors and genetic variations associated with AD and ASD are tabulated in Table 11.1 (Fu et al. 2010; Caramelli et al. 1999; Sokol et al. 2011; Crehan and Lemere 2016, Westmark and Malter 2007; Stigler et al. 2009; Rylaarsdam and Guemez Gamboa 2019; Bowers and Konopka 2012; Chen et al. 2020; Griciuc and Tanzi 2021).

Apart from the direct role of several genes in AD and ASD pathogenesis, lipid peroxidation (LPO), the end product of reactive oxygen species (8-isoprostane F2 α) attack, is another marker of ASD (Ming et al. 2005). Due to the lack of glutathione-producing ability of neuronal cells, the brain's capacity to detoxify ROS is decreased (Erden-İnal et al. 2002; Ono et al. 2001). Evidence has shown that extensive oxidative stress is a characteristic of AD brains and autistic children, in addition to the established pathology of senile plaques and neurofibrillary tangles in AD (Pratico 2008). Oxidative stress has been regarded as one of the contributing factors toward the pathogenesis of AD. Biopsies from AD brains have shown a significant reduction in mitochondria, while the mitochondrial DNA and proteins were seen increased in the cytoplasm and the vacuoles of brain cells. This suggests the degradation of brain cells due to oxidative stress (Hirai et al. 2001). Failure to resolve the inflammatory responses could lead to chronic inflammation and damage to the brain tissue, as observed in AD and ASD (Wang et al. 2015a).

11.2.3 Neuroimmune Dysfunctioning Associated with AD and ASD

Over the last few decades, understanding the underlying connection between the brain and immune function has undergone dramatic changes in perception of neurological degenerative diseases, mental disability, and several other related neuropathology comorbidities. A plethora of research defines the optimal functionality of the brain concerning the immune system, provided that the circulating immune and its response are needed to be tightly controlled, to understand the brain pathologies and the optimal effect that are directly or indirectly dependent on their type, location, activity, and other possible factors (Schwartz et al. 2020). Approximately one out of six brains of autistic patients show signs of immune cell infiltration in postmortem studies (Bailey et al. 1998).

Several in vivo model studies show an abnormal behavioral expression of natural killer cells/cytokines and its development in the blood plasma of AD and ASD patients especially interleukins (IL-1, IL-2, IL-4, IL-6, IL-8, IL-12, IL-13, IL-15, IL-1β, and CD8 antigen; Wang et al. 2015a, b; Ashwood et al. 2011; Stigler et al. 2009; Singh 1996; Lahiri et al. 2021). Lee et al. (2006) reported that the proportions of both CD4+ and CD8+ T-cells that associate with the production of interferon (IFN)-g and IL-2 were found to be significantly reduced; on the other side, CD4+ and CD8+ T-cells that produce IL-4 were significantly elevated in 20 ASD children in comparison to normal (Lee et al. 2006). Alteration in cytokine level is directly or indirectly associated with the dysfunction in the blood-brain barrier (BBB) system of the CNS (Noriega and Savelkoul 2014). Elevated ChAT activity and the presence of microglial cells in the basal forebrain and the immature CNS are potent markers of

Table 11.1 Genes implicated in AD and ASD

Gene	Source product	Function	Major diseases
APOE	Apolipoprotein E	Cholesterol trafficking	AD, ASD, CVDs
APP	β-Amyloid precursor protein	Neurite outgrowth and cell adhesion	AD, ASD
C4B	Complement cascade gene 4	Provides defense against foreign pathogens, autoimmunity	ASD, AD, dementia
FN1	Fibronectin 1	Blood clotting, wound healing	ASD, AD
NFTs	Neurofibrillary tangles	Microtubule stabilization	AD, tauopathies
Low plasma ApoA1	Apolipoprotein A1	Cholesterol removal	AD, CVDs
apoB-100	Apolipoprotein B100	Cholesterol efflux	ASD, diabetes
BDNF	Brain-derived neurotrophic factor	Neurotrophin, neuropreservation	Mental retardation syndrome, late-onset AD, ASD
COMT	Catechol-O-methyltransferase	Degrades catecholamines such as dopamine, epinephrine, and norepinephrine	Parkinson, ASD, AD
FHR1	Complement factor H-related protein	Complement activation	Uremic syndrome, autoimmune diseases, ASD, AD
FMR1	Fragile X mental retardation protein (FMRP)	Regulation of mRNA translation	AD, fragile X syndrome
HLA-A	Major histocompatibility complex, class I, A	Part of the major histocompatibility gene complex	AD, autoimmune diseases, rheumatoid arthritis, etc.
PTEN	Phosphatase and tensin homolog	Tumor suppressor phosphatase, regulation of neuron	Cancer, ASD
RELN	Reelin	Regulates neuronal migration and neuroplasticity in the brain	Cerebellar hypoplasia, AD, ASD
SLC6A4	Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4, HTTP	Intracellular serotonin transport	AD, ASD,
CLU,	Clusterin	Protein folding	Neurodegenerative diseases, cancer, AD, ASD, aging
TREM2,	Triggering receptor expressed on myeloid cells 2	Scaffold folding, signal transduction, regulation of interleukin-6 production	AD, ASD, dementia

(continued)

Table 11.1 (continued)

Gene	Source product	Function	Major diseases
PICALM,	Phosphatidylinositol-binding clathrin assembly protein	Protein coding and folding	Leukemia, AD
TNF	Tumor necrosis factor	Immune activation	Cancer, AD, ASD
PS-1 and 2	Presenilin 1 and 2	Generation β-amyloid, APP,	AD, ASD, cancer
NLGN-1,	Neuroligins	Amyloid β binding, an integral component of membrane	AD, ASD
SYN-1 and 2	Synaptic vesicle cycling proteins synapsin-1 and 2	Transporter activity, regulation of neurotransmitter secretion	Rett syndrome, AD, ASD
SCN2A	Sodium voltage-gated channel alpha subunit 2	Encode ion-exchange channel	Epilepsy, AD, ASD
CACNA1S	Calcium voltage-gated channel subunit alpha1 S	Provides instruction for making calcium channel	Epilepsy, AD, ASD
CACNB-2	Calcium voltage-gated channel auxiliary subunit beta 2	Encodes auxiliary calcium channel, trafficking to the plasma membrane	Brugada syndrome, epilepsy, AD, ASD
KCNQ-3 and *5*	Potassium voltage-gated channel subfamily Q members 3 and 5	Provides instruction in the making of potassium channel	AD, ASD, benign familial neonatal epilepsy
SHANK-3	Multiple ankyrin repeat domains 3	Protein folding, scaffold protein binding, regulate synaptic depression, synapse formation	AD, ASD, schizophrenia
FOXP2	Forkhead box P2 located on 7q31 chromosome expressed during mid-gestation (a critical time point in brain development)	Associated with language, speech, motor behavior during speech. Forced expression of FOXP2 in human neuronal cells and the human fetal neural progenitor cells resulted in concomitant repression of CNTNAP2, MET mRNA, and protein. (Bowers and Konopka 2012)	Pathophysiology of ASD

ASD (Hagberg et al. 2012; Pratt et al. 2013). Apart from this, genome-wide association studies (GWAS) reveal microglia and cytokines influence the expression of several genes known to be linked with AD pathologies (Ji et al. 2019; Villegas-Llerena et al. 2016; Karch and Goate 2015). Peroxisome proliferator-activated receptors (PPARα, β, or δ) stimulate inhibitory proteins such as nuclear factor-kappa β implicated in the expression of pro-inflammatory cytokines and chemokines promoting AD progression (Delerive et al. 2000; Lawrence 2009). Deficits of transforming growth factor beta-1 (TGF beta-1) could significantly contribute to

neuroinflammation and immune deregulation in ASD and AD (Ashwood et al. 2011). In a study by Shaftel et al. (2007), overexpression of IL-1 promotes Aβ plaques in AD patients.

11.2.4 Immunotherapy Associated with AD and ASD

Dysfunctioning in the immune system which is the underlying cause of AD and ASD led researchers to investigate immune-based therapies. As the immune-privileged organ, the brain posits a huge challenge for ASD and AD in the field of immunotherapy. Recently, several immune therapies mainly focus on the clearance of plaque deposited due to β amyloid (Aβ) employing several mechanisms. The transfer factor is a leukocyte lysate that stimulates an immune response against foreign bodies such as bacteria, fungi, and viruses. Several reports manifest the leukocytes mediated transfer factor (TF) based immunotherapy. In a study person infected with congenital CMV and ASD showed improved motor skills such as social behavior and interaction upon treatment with TF (Stubbs and Magenis 1980). A similar study was also reported by Singh et al. (1988) where 8 autistic patients were treated with TF. Six out of eight patients showed improvement in sleep, speech, and attention (Singh et al. 1988). In a subsequent study to ascertain TF's role, 10 (45%) out of 22 patients showed behavioral changes and improved IQ upon treatment with TF (Fudenberg 1996) after undergoing the Symptom Severity Score Average (SSSA) test.

Choroid plexus (CP) epithelial cells help in selective accession of immune cell access; leukocyte trafficking is found to be impaired in animal brain models and AD. Several independent in vivo studies have shown that the circulating monocyte and immune-regulatory leukocytes can remove misfolded or unfolded protein (Aβ plaques, tau proteins) hence maintaining the inflammatory milieu and synaptic neuron structure and reducing gliosis (Schwartz et al. 2019).

11.2.4.1 Immunotherapeutic-Based Drug Considered for Clinical Application in Autism.

11.2.4.1.1 Intravenous Immune Globulin

Intravenous immune globulin (IVIG)-based ASD treatment showed striking behavioral improvement in several studies. In a study out of 19 autistic children, one had markedly improved, four had adequately improved, while five showed minimal change (Gupta 1996). These patients have better vision, improved socio-vocabulary behavior, echolalia damage, and enhanced articulation (DelGiudice-Asch et al. 1999).

In an alternative study, four of the eight with regressive ASD treated with IVIG-based treatment showed modest progression in hyperactivity and attention, although the main symptoms showed no change. Simultaneously, a child with severe regressive ASD demonstrated a substantial enhancement in core autistic symptoms (Plioplys 1998). An oral human immunoglobulin study conducted on 12 youth

with ASD showed a better behavioral response after 8 weeks of treatment in 6 of 12 (50%) patients (Woods 2012).

11.2.4.1.2 Prednisone

Prednisone is a synthetic glucocorticoid used to treat autoimmune and inflammatory conditions due to its immunosuppressive effect. An open-label study examined 12 subjects with a pervasive developmental disorder for 16 weeks to use prednisone to treat the pervasive developmental disorder. However, six subjects showed progress in language abilities, with parents and teachers reporting subjective improvements in attention, purposefully directed behavior, and receptive emotional abilities (Stigler et al. 2009).

11.2.4.1.3 Naltrexone

Positive effects of steroid treatment were observed in the case of autism (Chez and Guido-Estrada 2010). Considering the effects that endogenous opioids have on immune function, 12 autistic children were treated with 12 antagonist naltrexone using a double-blind, placebo-controlled, crossover design. Patients on naltrexone demonstrated significant improvement in behavioral symptoms. No changes among naltrexone and placebo were found on the Childhood Autism Rating Scale. Seven children with the maximum noticeable enhancement were considered "respondents." A decrease in the suppressor (CD4 CD8 +) subset, with an increase in the sub-number of T-helper (CD4 + CD8) and normalization of the CD4/CD8 ratio after naltrexone treatment, was found in respondents. The responses exhibit beta-endorphin levels associated with the dispersal of the NK cell population during NACX cell treatment (Scifo et al. 1996).

11.2.4.1.4 Pentoxifylline

Pentoxifylline, an immune modulator, has been studied as a possible treatment for autism (Stigler et al. 2009). The drug prevents the production of certain cytokines, such as TNF-α and IFN-γ. Pentoxifylline was found to be successful in treating autism in many studies (Marchezan et al. 2018).

11.2.4.1.5 Vancomycin

Recently, antibiotic therapy in autism has been investigated. Several reports suggest that after repeated broad-spectrum antibiotic usage, the intestinal clostridial species may be responsible for developing autism in children. An open-label study with oral vancomycin was performed on 11 children with diarrhea and retrograde-onset autism. A study therapist completed the behavioral and communication rating scales on the respective child. Eight (80%) out of ten children treated showed improvement. All children's ratings returned to baseline soon after cessation of vancomycin treatment (Kang et al. 2017).

11.2.4.1.6 Vasopressin

The arginine vasopressin (AVP) signaling pathway is the most common pathway for the treatment of autism spectrum disorder (ASD). Various preclinical studies stated

the importance of AVP physiology, related to social functioning in many mammalian species. Research suggests that AVP signaling is associated with social impairment in children with ASD. The human gene for AVP-neurophysin II (NPII) is mapped to chromosome 20p13; multiple genetic loci within the AVP region can affect the progression of ASD, including childhood aggression (Hendaus et al. 2019).

11.2.4.1.7 Selective Serotonin Receptor Inhibitors (SSRIs)

Reports suggest that 21–32% of ASD children and adolescents with SSRIs were on prescribed medication is inconclusive evidence for SSRIs efficacy. The efficacy of four SSRIs (fluvoxamine, fluoxetine, citalopram, and fenfluramine) was investigated for ASD. Nine randomized clinical trials involving 320 participants were evaluated, reporting 17 different outcomes. Most of the data were unsuitable for meta-analysis, except for the proportion of improvements on the Clinical Global Impression-Improvement Scale for 2 trials of fluoxetine and fluvoxamine in adults who underwent SSRI placebo (relative risk, 12.58; 995% CI, 1.77–89.33). One of these studies also showed improvement in aggressive behavior measures, and another small study of adults showed improvement in anxiety. Citalopram confirmed no positive effect on the largest high-quality test in children. The benefits of SSRIs for ASD in children and adults was not restricted. Currently, SSRIs are prescribed "off-label" to treat children with autism (Posey et al. 2006).

11.2.4.2 Immunotherapeutic-Based Drug Considered for Clinical Application in the Case of Alzheimer's

11.2.4.2.1 Bapineuzumab

Bapineuzumab is a humanized monoclonal antibody that reduces brain fibrillar amyloid in AD patients (Sperling et al. 2012). However, it was associated with a risk of vasogenic edema and microhemorrhage (ARIA). The 3D6 is the murine precursor of humanized bapineuzumab, which has been reported to enter the transgenic mice model's brain, decorate the plaques, and induce Fc receptor-mediated phagocytosis (Bard et al. 2000). Several clinical studies have been conducted which indicate a reduction in fibrillar amyloids in the brain of AD patients. A meta-analysis based on clinical studies suggests a lack of bapineuzumab's clinical efficacy and its association with adverse effects (Abushouk et al. 2017). Therefore, the use of bapineuzumab to treat AD patients is not recommended and can only be reconsidered after re-evaluating its efficacy in a combinatorial formula.

11.2.4.2.2 Solanezumab

Solanezumab, another humanized IgG1 mAb, recognizes and targets a middle region (residues 16–26) amyloid peptide epitope (Farlow et al. 2012; Siemers et al. 2016). The murine precursor (m266) of the antibody binds tightly to monomeric amyloid peptides but not to aggregates or fibrils (DeMattos et al. 2001, 2002). Solanezumab effectively reduces amyloid in transgenic mice and does not carry the risk of ARIA

like the bapineuzumab. Here, the proposed mechanism of action is the peripheral sequestration of a monomeric amyloid peptide, i.e., peripheral sink effect.

11.2.4.2.3 Crenezumab

Similar to solanezumab, crenezumab is another humanized mAb that recognizes and targets a midsequence (residues 13–24) amyloid peptide epitope. However, it differs from solanezumab in that it possesses an IgG4 backbone. The IgG4 isotype helps microglial phagocytic activity without raising cytokine storm (Adolfsson et al. 2012) which contributes to neurotoxicity as well as ARIA (Ultsch et al. 2016). In vitro studies report that crenezumab efficiently binds to amyloid fibrils and oligomers but to a lower extent to monomers (Adolfsson et al. 2012). The epitopes recognized by solanezumab and crenezumab overlap and therefore exhibit crossreactivity. Aβ residues 21–26 adopt α-helical structure when bound to solanezumab, whereas residues 21–24 exhibit random coil structure when bound to crenezumab. The occurrence of α-helical epitope only in monomeric forms of Aβ but not in aggregates explains solanezumab's preference to bind monomer.

11.2.4.2.4 Gantenerumab

Gantenerumab, the first fully human IgG1 anti-Aβ mAb, can bind to conformational epitopes that encompass both the N-terminus (residues 3–12) and midsequence (residues 8–27) epitopes and show high affinity for fibrils. Early studies based on PET (positron emission tomography) demonstrated that gantenerumab significantly reduced brain amyloid plaques by recruiting microglial cells (Bohrmann et al. 2012). Similarly, SAR228810 is also a humanized antibody that recognizes a particular conformational epitope that allows specific binding to protofibrils and fibrils.

11.2.4.2.5 Ponezumab

Ponezumab is a human IgG2 mAb that targets the Aβ C-terminus (residues 30–40) (La Porte et al. 2012). The IgG2 isotype has lower immune potential (Landen et al. 2013) limiting their clinical efficacy; therefore, ponezumab production was discontinued after a few trials.

11.2.4.2.6 BAN2401

BAN2401, a humanized IgG1 mAb, specifically binds to soluble Aβ protofibrils. This antibody was developed by E22G arctic mutation in the APP and has shown an efficient reduction of Aβ protofibrils in the brain and CSF of tg-ArcSwe mice (Tucker et al. 2015). Multiple clinical trials are going on, and BAN2401 has been reported to show no ARIA cases, the significant limitations of bapineuzumab (Lannfelt et al. 2014).

11.2.4.2.7 Aducanumab

Aducanumab, a human IgG1 mAb, selectively targets Aβ aggregates, including soluble oligomers and insoluble fibrils (Sevigny et al. 2016). It targets the N-terminus (residues 3–6), which forms a conformational epitope absent in monomers. Analogs of this mAb exhibited the potential to cross BBB, bind

parenchymal Aβ, and reduce soluble as well as insoluble Aβ (Sevigny et al. 2016). So far, several clinical trials have been conducted using mAbs. Still, these mAbs persist in limitations regarding their production, lower tissue penetration, and adverse effects associated with inflammatory reactions and CAA-associated microhemorrhage (Racke et al. 2005). The lack of specificity to the toxic pathological Aβ oligomers is the major limitation of these passive therapies. Therefore, it can be carefully contended that passive therapeutic approaches have limited efficacy in symptomatic AD.

11.2.4.2.8 Antibody Fragments

Different formats of recombinant antibody fragments, such as single-chain fragment variable (ScFv), fragment antigen-binding (Fab), single-domain antibody fragments (VHH or sdAbs), bispecific antibodies (BsAb), gamma bodies, and intrabodies, are currently being investigated as therapeutics for AD. These are preferred over conventional full-length mAbs owing to their great specificity, higher affinity, stability, solubility, and reduced immunogenicity (Manoutcharian et al. 2017).

The ScFvs

The ScFvs are the smallest antibody fragments (VH and VL linked with a linker). These antibody fragments show increased stability as well as affinity (Frenkel et al. 2000; Malone and Sullivan 1996). ScFv can be delivered and distributed all over the brain via intracerebral, intranasal, or virus-mediated routes (Campana et al. 2009; Donofrio et al. 2005; Federoff 2009; Filesi et al. 2007). They are packaged in small viral vectors like recombinant adeno-associated virus (rAAV) and injected into the CNS. The first ScFv-based anti-Aβ antibody, 508F (Fv), was derived from the monoclonal IgM 508 antibody. This fragment demonstrated efficient disaggregation of Aβ fibrils and also reduced toxicity in cultured PC-12 cells. Similarly, N- and C-terminal binding ScFvs were produced and selected using naive human ScFv phage library with Aβ1–28 and Aβ1–40, respectively (Liu et al. 2004; Robert et al. 2008). Only the ScFv against N-terminal could inhibit Aβ aggregation in vitro (Liu et al. 2004). Other novel fragments called catabodies have been developed. These catabodies are ScFv fragments generated by affinity maturation of the corresponding parent mAb with improved catalytic activity. They catalyze the proteolysis of Aβ and reduce the accumulation of toxic amyloid in the brain. The first catabody, Asec-1A, inhibited the aggregation of Aβ and reduced Aβ toxicity on human neuroblastoma cells (Kasturirangan et al. 2010). Similarly, a bispecific tandem ScFv produced by combining iBSEC1 and Asec-1A showed inhibition of amyloidogenic APP processing and enhanced Aβ proteolysis (Boddapati et al. 2012).

Fab Fragments

Fab fragments contain one heavy and one light chain with binding avidity lower than IgG but affinity parallel to it. These are small in size and also stable when compared to ScFvs. Tammer et al. (2002) produced a recombinant Fab (rFab) against the central region of Aβ derived from the parent hybridoma 1E8. This rFab was an efficient binder of amyloid plaques. This rFab retained the ability to inhibit fibril

formation and associated toxicity with a strong affinity (Kd-6 nm) for Aβ, determined by surface plasmon resonance measurements (Robert et al. 2008, 2010).

Bispecific Antibodies (BsAbs)

A highly innovative approach, the molecular Trojan horse technology (Pardridge 2008) has been employed to generate fusion proteins called BsAbs against AD. These BsAbs contained binding sites for Aβ peptide and for the insulin/transferrin receptor (IR/TfR), which are highly expressed on the BBB. The central part of the BsAb comprising CH2–CH3 domain of the mAb provides the binding site for the FcRn receptor expressed on the BBB (Robert and Wark 2012).

Gamma Bodies

Gamma bodies are grafted amyloid-motif antibodies. They are designed based on the principle that the amyloidogenic motifs of one Aβ peptide interact with identical motifs of adjacent Aβ monomers forming stacks of parallel β sheets (Lührs et al. 2005; Perchiacca et al. 2012). This homotypic interaction between peptide motifs induces Aβ fibrillation, and this phenomenon has been exploited for antibody engineering to recognize specific Aβ oligomers and fibrils. A small amyloidogenic peptide (6–10 residues) from Aβ-42 is grafted into the complementarity determining regions (CDRs) of the VH domain that can recognize soluble Aβ oligomers and fibrils. The gamma bodies which display the Aβ motif (18VFFA21) react with Aβ fibrils. The central hydrophobic segment 18VFFA21 form β sheets during the formation of fibrils from soluble Aβ oligomers (Lührs et al. 2005; Malone and Sullivan 1996). Gamma bodies specific to fragments Aβ12–21, Aβ15–24, and Aβ18–27 can readily recognize the Aβ18–21 motif present in β sheet but not insoluble Aβ oligomers. Therefore, the β sheet development by the Aβ18–21 motifs is the crucial structural modification during fibril formation from Aβ oligomers (Perchiacca et al. 2012). However, gamma bodies displaying C-terminal motif (34LMVGGVVIA42) recognize and bind both the oligomer and fibrils but weakly with Aβ monomers (Ahmed et al. 2010; Zhang et al. 2013). Consequently, these gamma bodies neutralize toxicity associated with both the conformers.

Intrabodies

Intrabodies are the intracellularly expressed antibody fragments that recognize and bind molecules within the cell (Cardinale and Biocca 2008; Miller and Messer 2005). The intrabody ScFv-β1 developed to recognize the N-terminal region near the β-secretase cleavage site demonstrated a significant reduction in Aβ generation in APP overexpressing human embryonic kidney cells (Paganetti et al. 2005). This was further improved when the KDEL sequence was incorporated which facilitated expression specifically in the endoplasmic reticulum. ScFv-β1 acts by shielding the cleavage site for β-secretase which facilitates the inoffensive α-secretase-induced cleavage of APP (Sudol et al. 2009). In AD, the Fc region of antibody plays a significant role in eliciting adverse reactions which include meningoencephalitis and cerebral hemorrhages. Strategies that help lower the affinity of Fc to the Fc receptor (FcγR) present on immune cells and inhibit complement activation through c1q

binding are being worked upon. Point mutation for deglycosylation of the asparagine at 297th position to alanine or glutamine, or replacing leucine with alanine in the lower hinge region (L234 and L235), helped lower the Fc-FcγR interactions (Alegre et al. 1994).

11.2.5 Immunotherapy-Based Common Medication for AD and ASD

Despite bundles of promising research from several decades, no effective medication for AD and ASD exists. This might be due to the huge interconnection and complex interplay of several genes/proteins in defining and staging AD and ASD. Drugs like risperidone, thioridazine, risperidone, olanzapine, valproate, and serotonin are widely used in treating AD patients (Lauterbach et al. 2010). Several ongoing AD medications are currently being used to treat ASD such as rivastigmine, donepezil, tacrine, galantamine, and memantine. Although FDA has not solely approved its use in the treatment of ASD, these drugs show improvement in overall ASD behavior like motor skills, expression, receptive language, social interaction, eye contact, and many more (Rossignol and Frye 2014) with minor and long-term side effects. This demands second-generation research that offers significant advantages in terms of decreased cognitive and neurological impairment and reduced short- or long-term side-effects (Table 11.2).

11.3 Dissimilarity in Alzheimer's Disease and Autism

In the previous sections, much has been discussed, highlighting the features expected in AD and ASD. Both conditions involve the build-up of proteins in the brain and fueled by infectious waste, including neurotoxins causing the ultimate neurological dysfunction. Several similarities among the two diseases are also considered as twin similarities (https://alzheimerdisease.tv/diagnosis/autism/).

However, when the turn of differences between the two comes, the most popular aspect we consider is the age factor, which is undoubtedly the biggest difference. ASD is a neurodevelopment disease in kids, while AD is a neurodegenerative disease of elderly people. Due to this crucial difference, ASD is often called AD of a child, and AD is known as ASD of mature adults (Nasrat et al. 2017b).

Not discussed much, but there are still other notable differences between them, which makes us say the twin similarity is not identical. These differences include:

1. Autism is a brain deformity that controls a person's potential to correlate, communicate, and relate to other people. On the other hand, Alzheimer's disease is a chronic, progressive, and prevalent most common age-related neurodegenerative disease (Nasrat et al. 2017b).
2. Autism is identified by a decrease in cognitive and social functions associated with loss of already developed skills, while Alzheimer's is a progressive disease

Table 11.2 The common conventional drugs used in the treatment of AD show an effective response in ASD

Conventional drugs	Administration	Response	Side effects	References
Haloperidol	Oral, nasal spray, intramuscular, intravenous	Reduction in stereotypies, behavioral improvement	Pyramidal side effects, blurred vision (long-term effect)	Campbell et al. (1990)
Risperidone	Oral, deep intramuscular	Reductions in repetitive behavior, aggression, anxiety/nervousness, and depression	Weight gain, nausea, restlessness, vomiting	McDougle et al. (1998)
Olanzapine	Oral, intramuscular	Reductions in repetitive behavior, aggression, anxiety/nervousness, and depression	Weight gain, restlessness	Potenza et al. (1999)
Selective serotonin reuptake Inhibitors	Oral, intramuscular	Disabling anxiety, obsessional and repetitive behavior, and the tendency of self-injury	Weight loss, dizziness, headache, etc.	Fatemi et al. (1998)
Opiate antagonists – Naltrexone	Oral, nasal spray, intramuscular, intravenous	Reducing overactivity, promotes social engagement, and decreases self-injurious behavior	Trouble sleeping, dizziness, joint pain, etc.	Willemsen-Swinkels et al. (1995)
Aripiprazole	Intramuscular	Reduces irritability	Nausea, vomiting, light-headedness, blurred vision, weight gain	Elbe and Lalani (2012)

hallmarked by cognitive disorders associated with loss of memory functions (Li and Zhou 2016; Plassman et al. 2007).

3. Alzheimer's is more prevalent in females than males, while autism is more frequent in boys than girls (Hestvik et al. 2010; Leandro et al. 2005).
4. Alzheimer's could take some years to develop, while autistic disorder could have a fast onset to grow. Autism is a neurodevelopmental disorder occupying the critical period of development of centers responsible for skills during early childhood (Nasrat et al. 2017c); toxins could compromise these developing centers in a short duration, affecting their development faster. While Alzheimer's is a neurodegenerative disease targeting already developed brain centers among old-age people (Nasrat et al. 2017a), degeneration of these centers is a delayed process needing, therefore, some years to exert its effect.

11.4 Future Prospects Based on Lipoprotein-Based Immunotherapy for AD and ASD

Studies in humans and in vivo and in vitro models support the hypothesis that circulating HDL has vasoprotective properties, provides resilience to cerebrovascular dysfunction in AD, removes Aβ plaque from the brain endothelial cells via active (Montañola et al. 2016), and reverses cholesterol transport mechanism by involving various receptors such as p-glycoprotein, LDL receptor-related protein (LRP1), and LDLR. Several studies show that the low level of apoA1, the major component of HDL (Zuliani et al. 2010), elevated total cholesterol, and LDL/apoB levels correspond to increased neuritic plaque density associated with a more severe form of AD (Merched et al. 2000; Saczynski et al. 2007; Bates et al. 2009). Several cross-sectional studies reported overexpressed apoB in neuronal degenerated cells/tissue of transgenic mice (Bereczki et al. 2008, Caramelli et al. 1999) and lower serum apo-A1 and HDL-C levels in AD (Jansen et al. 2019; Kunkle et al. 2019). Other studies also reported dysregulation of cholesterol metabolism-associated genes, higher triglycerides (TG), lower HDL, and LDL/HDL ratio in ASD patients (Kim et al. 2010; Tierney et al. 2006; Hu et al. 2009). Smith-Lemli-Opitz syndrome (SLOS) is an inborn decrease in cholesterol synthesis associated with ASD symptoms (Aneja and Tierney 2008; Sikora et al. 2006).

Smith-Lemli-Opitz syndrome (SLOS), an inborn decrease of cholesterol synthesis associated with ASD, improves rapidly after cholesterol supplementation (Tierney et al. 2006). Besides, the expression level of apoB100 and apoA4 was found to be elevated in high- versus low-functioning ASD (Corbett et al. 2007). Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) mediates vascular inflammation through the regulation of lipid metabolism in the blood. Lp-PLA_2 inhibition showed promising therapeutic effects in Alzheimer's disease. Darapladib, a selective and orally effective Lp-PLA_2 inhibitor, has beneficial effects on the functional integrity of the BBB (Huang et al. 2020) and reduced the influx of plasma components into the brain tissue (Acharya et al. 2013). A phase II trial demonstrated that Lp-PLA_2 inhibition could benefit AD progression (Huang et al. 2020).

Rilapladib, another potent Lp-PLA_2 inhibitor, resulted in low levels of plasma CSF neurodegenerative markers, including albumin quotient (AlbQ), total tau (T-tau), P-tau181, and neurofilament light chain (NFL). Lp-PLA_2 inhibitors might result from preventing BBB breakdown in cerebral amyloidosis in an independent manner. Both darapladib and rilapladib were reported to be well tolerated with no major side effects observed (Shaddinger et al. 2014).

Furthermore, lipoprotein (HDL) ability to modulate cholesterol bioavailability and microdomains-enriched-glycosphingolipids is conserved evolutionarily, which affects the landscape of the cell involved in the innate/adaptive immune system, inflammation, and antigen presentation in several macrophages, cytokines, receptors, B and T cell activation, and their complex pathways (Norata et al. 2012). In reflection of the possible important role of lipoprotein and cholesterol in ASD and AD patients, large-scale clinical studies that manifest cholesterol supplementation need to be initiated. There are considerable shreds of evidence that define

HDL-based therapeutics' safety in clinical trials against ASD and AD. Such as in the prevention of AD-related neuroinflammation in mouse models and 3D bioengineered human arteries, HDL molecules due to their small size and penetration tendency have also been used as a drug carrier to overcome the issue of BBB penetrance during drug delivery. Reconstituted HDL carrying an Aβ-targeting drug enters efficiently in the brain of AD mice, reduces amyloidosis, and improves memory (Button et al. 2019). Thus, modulating ASD and AD-related neuroinflammation based on the lipoprotein-mediated immunotherapy approach could be an effective strategy to prevent damage to the CNS.

11.5 Conclusions

Immunotherapy is proving increasingly important for treating AD and ASD, but it should be approached cautiously. Clinical trials and experimental systems have demonstrated that cellular and humoral immune responses can be effective in amyloid-β clearing. The attraction of immunotherapy for AD and ASD lies in its ability to immunize large areas of the aging population to treat or prevent these common neurological disorders' dreadful effects. In inference, there is considerable and robust evidence to recommend that active immunotherapy has the potential to treat AD and ASD.

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Alzheimer's Disease (AD): Physiological Barriers for Therapy and Nanotechnological Applications in Treatment

12

Mohd Ahmar Rauf, Katyayani Tatiparti, and Arun K. Iyer

Abstract

Neurodegenerative diseases are becoming more common in the people of old age. Numerous complications have occurred in the treatment of neurodegenerative diseases, some of which are multi-systemic in nature. Since the structure, efflux pumps, and expression of the blood-brain barrier's (BBB) metabolism are limited, traditional drug delivery systems are ineffective for treating neurodegenerative disorders. Nanotechnology has the potential to significantly improve neurodegenerative disease treatment by bioengineered systems that interact with biological systems on a molecular level. This chapter discusses the applications of nanoparticles in the treatment of Alzheimer's disease.

Keywords

Alzheimer's disease (AD) · Blood-brain barrier (BBB) · Nanoparticles (NPs) · Liposomes · Therapeutics

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12.1 Introduction

The brain accounts for approximately 2% of body weight and consumes approximately 20% of coronary blood supply and 25% of total oxygen and glucose supply (Zlokovic 2011). The presence of 100 billion capillaries and a complex network of intercellular communications through the release of neurotransmitters and neuromodulators in cohort with the synaptic potentials is responsible for brain functioning (Abbott et al. 2006; Pardridge 2003). These brain activities require continuous movement of ions and other molecules across the blood-brain barrier (BBB). BBB is a selectively permeable membrane that protects the brain and maintains the integrity of its functions. It separates the blood and brain tissue. An intact BBB is vital to keep the brain tissue in a healthy state. It is often found disrupted in most of the central nervous system (CNS) pathologies such as Alzheimer's disease (AD), brain cancers such as glioblastoma multiforme (GBM), Parkinson's disease (PD), multiple sclerosis (MS), or amyotrophic lateral sclerosis (ALS) (Krol et al. 2013) which contribute to almost 12–15% of deaths globally. Successful treatment of these conditions depends on the extent of crossing BBB by the therapeutics. However, most of the noninvasive therapeutics for these conditions have failed at the preclinical and clinical trials. This is because the brain allows only a tiny percentage (2–3%) of small molecules across the BBB (these, in turn, show very low absorption by brain parenchyma), while large molecules are all excluded (Pardridge 2007) because of their insignificant penetration across BBB.

The unique protective ability of the BBB can be attributed to its anatomical structure, physiological functions, and enzymatic and immunological activities. These are discussed briefly below. A thorough state-of-the-art understanding of these aspects of the brain and BBB will equip scientists worldwide to better target the nanotherapeutics to the brain for successful treatment of CNS conditions.

12.2 Anatomy and Physiology of the Brain

The brain consists of a unique composition of its blood-brain parenchyma barrier that is different from other parts of the body because of three specialized, tightly regulated vascular barriers (Chen and Liu 2012). These barriers can be categorized as follows: (1) arachnoid barrier; (2) blood-cerebrospinal fluid barrier; and (3) blood-brain barrier (Abbott 2004). A diagrammatic representation of these barriers is shown in Fig. 12.1.

12.2.1 Arachnoid Barrier

The brain is made up of three layers of protection composed of connective tissue called the meninges. They are called the dura mater, arachnoid mater, and pia mater. Their primary function is protecting the brain and containment of cerebrospinal fluid (CSF) (Furtado et al. 2018). The cells forming the arachnoid mater are epithelial and

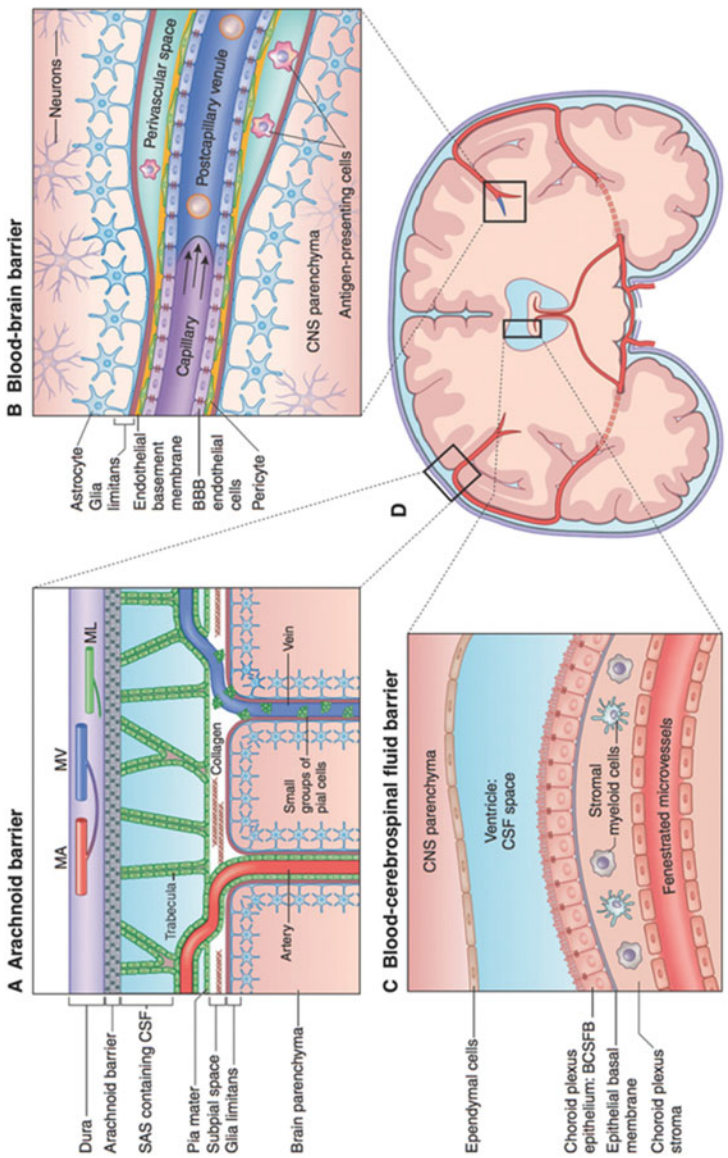

Fig. 12.1 The barriers in the brain: (**a**) arachnoid barrier; (**b**) BBB; (**c**) blood-cerebrospinal fluid barrier; (**d**) brain section. BBB is the closest to the neuronal tissue and is the best target for delivering therapeutics. (Adapted with permission from Engelhardt et al. (2017))

form the arachnoid barrier. This barrier is relatively avascular and has a low surface area of the total BBB. For therapeutics delivery, this barrier is not approachable because of the low surface area.

12.2.2 Blood-Cerebrospinal Fluid Barrier

This membrane separates the brain from the cerebrospinal fluid. CSF is developed in the choroid plexus of the brain's lateral ventricles. The epithelial cells forming the choroid plexus forms this barrier. Since the CSF is replenished every 4–5 h, the brain flushes out any medication delivered through this barrier. Hence, it cannot present itself as a good target for therapeutics.

12.2.3 Blood-Brain Barrier

This barrier is the closest to the neurons. It consists of a very intricate network of capillaries. BBB is comprised of the brain microvessel endothelial cells (BMEC or BMVEC or BEC). BMEC separates the blood compartment from the interstitial fluid (ISF) of the brain. The isotonicity and composition of the ISF are maintained by transport of various molecules and ions across BBB for the brain's optimal functioning. It is responsible for the transport of nutrients to the brain. It is characterized by its very efficient efflux pumps that eliminate wastes out of the brain. It also has a role in regulating and maintaining neurotransmitters at the periphery of the brain, immune surveillance of the brain, and the inflammatory responses to the brain's invasion (Abbott et al. 2010). Hence, it is a dynamic barrier that protects the brain aggressively. The BBB function is due to a collective action of BMEC and other cells such as astrocytes, pericytes, microglia, vascular smooth muscles, oligodendrocytes, and so on, which communicate with each other constantly in complex pathways, thus regulating its permeability (Banks 2016; Neuwelt et al. 2011). This cohort of cells is called the neurovascular unit (NVU). Many of these complex communicative pathways of the NVU are yet to be understood.

12.3 Blood-Brain Barrier (BBB)

The blood-brain barrier can be described in detail by defining the composition of NVU and the physical structure as follows (Fig. 12.2).

12.3.1 Composition of the Neurovascular Unit (NVU)

12.3.1.1 Vascular Smooth Muscles

These muscles make up the arteries, arterioles, and veins of the brain and regulate blood vessel functions. They often take up the role of pericytes.

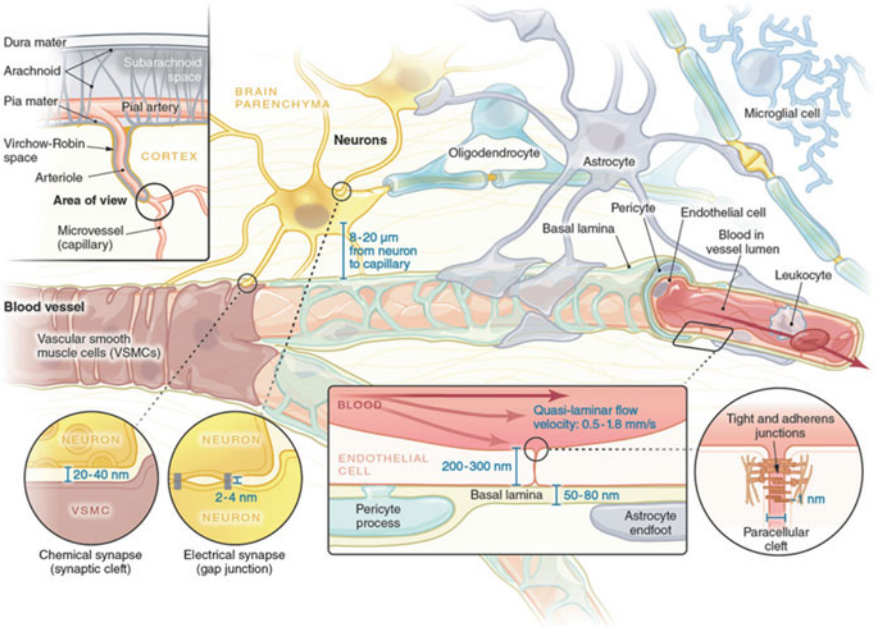

Fig. 12.2 The neurovascular unit of the blood-brain barrier. A crosstalk between various cells in the BBB elicits a highly protective and selective function of the BBB. (Adapted with permission from Furtado et al. (2018))

12.3.1.2 Pericytes

These cells surround the BMEC and enclose the brain's capillaries in the basal lamina of BBB, maintaining its integrity, homeostasis, and blood supply alongside regulating macrophages (Abbott 2013). They have an important role in maintaining tight junctions of the brain.

12.3.1.3 Astrocytes

These are star-shaped cells with perivascular end feet that support the BMEC (Ransohoff et al. 2003). They have a role in the permeability of the BBB. Astrocytes also express AQP4 water channels and the ion channels that maintain water and ion homeostasis in the brain. Apart from supporting the neurons, astrocytes also insulate the neurons, provide nutrition, and have a role in cytokine-mediated inflammatory responses (Zlokovic 2008).

12.3.1.4 Microglia

These cells represent the macrophages in the brain originating from the perivascular macrophages that cross BBB in the event of infection (Williams et al. 2001). Their main function is phagocytosis of the dead and diseased neural tissue. They produce pro-inflammatory factors such as lipopolysaccharide (LPS), tumor necrosis factor-α

(TNF-α), interleukin-1ß (IL-1ß), and reactive oxygen species (ROS) that can disrupt the BBB and its permeability (Didier et al. 2003).

12.3.2 Physical Structure of the BBB

BBB presents particular BBB properties attributed to the highly protective and selective nature of its functions. These prioperties include the following.

12.3.2.1 Tight Junctions

Tight junctions are composed of transmembranous intercalated particles formed by cytoplasmic proteins (such as claudins, occludins, and junctional adhesion molecules) and function as gates between BMECs. They have a pore size of approximately 1.4–1.8 nm (Zhang et al. 2016). Figure 12.3 illustrates the close junctions. Their function is to prevent different molecules from traveling paracellularly and to restrict their movement across the BBB to passive transport of molecules with a diameter of less than 1 nm (Sarin 2010). Each stimulus recycles these close junctions (Deli 2009). Claudin proteins are one of the primary cytoplasmic proteins involved in the formation of close junctions. The tight junctions formed

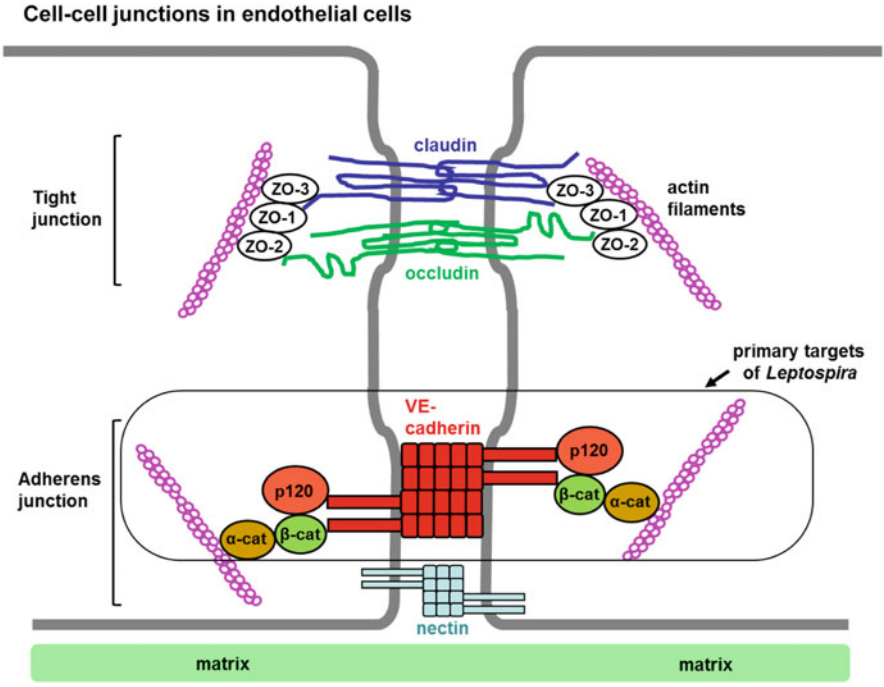

Fig. 12.3 The tight junctions and adherens junctions consisting of claudin, occludin, and intracellular zonula occludins (ZO) proteins. (Adapted with permission from Sato and Coburn (2017))

by claudins provide the BBB with a high transendothelial electrical resistance (TEER) of approximately 1500–2000 cm^2. Occludins and junctional adhesion molecules (JAM-A, B, C) are proteins that help maintain and promote the close junction and leukocyte movement across the blood-brain barrier (BBB) (Kooij et al. 2005). Tight junctions cooperate with cytoskeletal proteins such as actin and cytoplasmic proteins such as calcium-dependent serine protein kinase (CASK), zonula occludins proteins (ZO-1, ZO-2, ZO-3), and cingulin. Cytoplasmic proteins are categorized into first- and second-order adaptor proteins based on their ability to strengthen the connections between close junctions and the endothelial cell cytoskeleton.

12.3.2.2 Adherens Junction

These junctions are found closely placed near the tight junctions. They are composed of glycoproteins of the class calcium-dependent cadherins, primarily vascular endothelial cadherin (cadherin-5 or VE-cadherin) that adhere to the cytoskeleton of the BMECs via linker molecules such as platelet-endothelial cell adhesion molecule (PECAM), the catenins (α-, ß-, and γ-catenin), desmoplakin, and p120 catenin (Bhowmik et al. 2015). They mainly have a role in regulating intercellular interactions and paracellular permeability and microvascular integrity.

12.3.2.3 Apicobasal Polarity

The differences in the composition of the proteins of the tight junctions and adherens junctions, the distribution of the target receptors, secretions from the cells, and responses to stimuli between the luminal and abluminal sides of the membrane constituting BBB create a polarity on it that has an important role in maintaining the integrity of the BBB (Worzfeld and Schwaninger 2016).

12.3.2.4 Luminal Surface-Bound Glycocalyx

Glycocalyx is a carbohydrate-rich enclosure of the BMEC bound to it by glycoproteins and proteoglycans. It maintains the integrity of BBB due to the sialic acid component of the glycocalyx. It is responsible for the protection of BBB and regulating the movement of molecules across it (Yokel 2016).

12.4 Enzymatic Role of BBB

The BBB is described by an enzymatic activity that protects the brain from different molecules that pass through it by metabolizing them in endothelial cells (Pardridge 2005). These enzymes include monoamine oxidases and cytochrome P450 that can inactivate toxic substances. Apart from the BMECs, pericytes and astrocytes also possess enzymatic activity from peptidases, cholinesterases, and other such enzymes that protect the brain (Yi et al. 2014).

12.5 Immunological Activity of BBB

The immunological activity of the brain is very selective and unique (Ransohoff et al. 2003). There is very little presence of lymphatic vessels in the brain. It also lacks antigen-presenting cells (APCs) native to the region that elicit immune responses by identifying inflammatory molecules such as dT-cells (Wekerle 2002). Major histocompatibility complex (MHC) class II is expressed in certain microglia in the brain (Matsushima et al. 1994). Leukocytes, in the form of T-cells, are also extremely scarce in the brain. Thus, the brain's immunity is preserved mainly by the actions of BMECs, perivascular macrophages, microglia, brain T cells, and mast cells. Further, chemokines elicit the immune responses in the brain by recruiting T-cells during infections. These pro-inflammatory immune reactions, in turn, trigger the immunosuppressive mechanisms in the brain (Furtado et al. 2018).

12.6 Transport Mechanisms in BBB

As previously mentioned, endothelial transport is the primary route for molecules to enter the brain. It occurs through endocytosis into endothelial cells as well as transcytosis into the BBB's luminal and abluminal membranes. The BBB transports nutrients from the blood to the brain, including glucose, galactose, amino acids and monocarboxylic acids, nucleosides, amines, and vitamins, as well as growth factors, enzymes, and plasma proteins. The constant flow of ions and other solutes through the BBB maintains the brain's pH. Additionally, BBB efflux pathways are used to remove radioactive waste and metabolites. Due to the close junctions, the BBB allows for very little paracellular transport. There are very unique mechanisms that enable molecules and nutrients to pass through the BBB. The majority of these processes operate in a bidirectional fashion, bringing information into and out of the brain. However, some of these processes are constrained by the particle size requirements. A clever design of therapeutic delivery systems that exploit BBB mechanisms can be an effective strategy for increasing drug bioavailability. The different processes at work will be briefly discussed here (Fig. 12.4).

12.6.1 Types of Transport Pathways Across the BBB

12.6.1.1 Paracellular Transport

This mechanism occurs very low through pores in the BMECs upon stimulation in pathological conditions (Smith et al. 2016).

12.6.1.2 Passive Diffusion

This mechanism transports only lipophilic compounds. It is highly restrictive based on the molecular size (<500 Da) and the number of hydrogen bonds (9–10) (Lipinski et al. 2012).

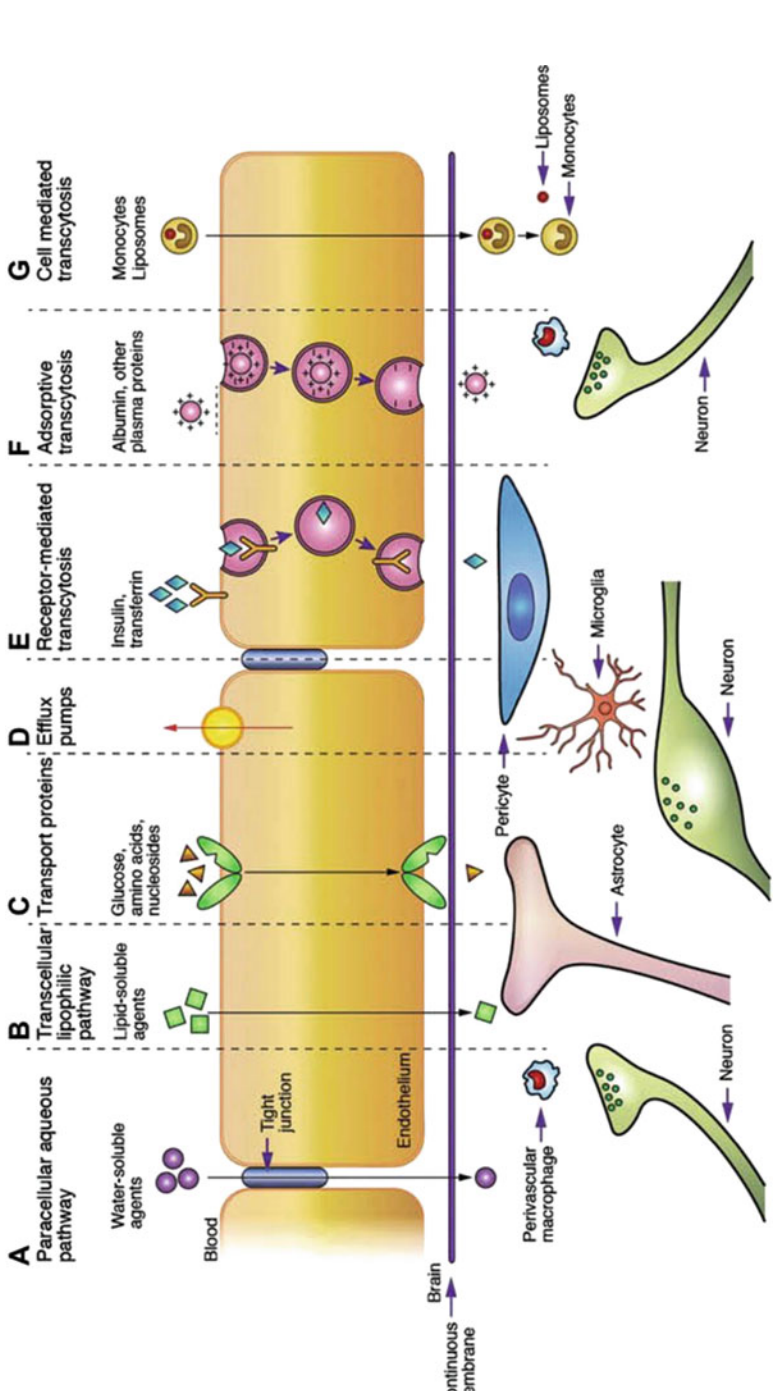

Fig. 12.4 The mechanisms of transport of various molecules across the BBB and the efflux pump. (**a**) Paracellular pathway—for transport of water-soluble molecules; (**b**) Transcellular pathway—for passive transport of lipid-soluble molecules; (**c**) Transport proteins—for bidirectional transport of endogenous molecules; (**d**) Efflux pumps—for removal of lipid-soluble molecules out of brain; (**e**) Receptor-mediated transcytosis—for transport of molecules through specific receptors; (**f**) Adsorptive transcytosis—for transport of molecules via electrostatic interactions of ligands with the cell membrane; (**g**) Cell-mediated transcytosis—for transport of molecules using endogenous cells such as monocytes. (Adapted with permission from Chen and Liu (2012) and Herda et al. (2014))

12.6.1.3 Carrier-Mediated Transport

This mechanism is responsible for endogenous molecule transport through specific transporters. The molecules' movement is determined by the concentration gradient and is accomplished by the use of assisted diffusion transporters (in the gradient's direction) or active transporters (against the concentration gradient). Glucose transporter 1 (GLUT1), excitatory amino acid transporter 1 (EAAT1), monocarboxylate transporter 1 (MCT1), and massive neutral amino acid transporter 1 (LAT1) have been identified as some of the most highly expressed transporters in the brain that are involved in the transport of glucose, amino acids, and other nutrients (Smith 2005; Ohtsuki and Terasaki 2007; Pardridge 1998).

12.6.1.4 Receptor-Mediated Transport

This mechanism facilitates macromolecule uptake through clathrin- or caveolin-mediated endocytosis. The macromolecules serve as ligands for unique receptors on the surface of the cells, forming the BBB such as LRP1, LRP2, and LDLR. Following this, BMECs form vesicles and endosomes, which release the contents of the vesicles into the brain. Intracellular proteins such as amphiphysin, endophilin, and various adaptins, dynamins, and rab proteins guide the transport of vesicles inside the cell (Bareford and Swaan 2007; Villaseñor et al. 2017). The clathrin-mediated endocytosis is responsible for the uptake of molecules with a diameter of 200 nm, while the caveolin-mediated endocytosis is responsible for the uptake of molecules with a diameter of up to 500 nm (Wohlfart et al. 2012).

12.6.1.5 Adsorptive-Mediated Transport

BBB is negatively charged because of the proteoglycans, which impedes some of the macromolecules' transport due to electrostatic interactions. Such molecules are endocytosed by adsorptive-mediated transport. The affinity of macromolecules to this pathway is much less, and hence the transport via this way is much less compared to receptor-mediated transport (Hervé et al. 2008). However, the vesicles formed in this path are much larger and can transport a higher number of macromolecules across the BBB.

12.6.1.6 Cell-Mediated Transport

This mechanism is particularly successful at transporting molecules across the BBB by immune cells such as macrophages and monocytes (Batrakova et al. 2011). This mechanism is sometimes referred to as a "Trojan horse" technique because it utilizes natural processes such as chemotaxis and diapedesis to recruit immune cells to deliver therapeutic agents to the site of action. The benefit of this pathway is that it can carry molecules as big as 1.2μm to the brain.

12.7 Efflux Mechanisms of the BBB

Efflux processes aid in the elimination of waste and other potentially toxic substances from the brain. Efflux transporters protect the brain's interstitial fluid (ISF) from adulteration. These transporters are found on both the luminal and abluminal BBB membranes. They are extremely active and can rapidly expel foreign particles from the brain. The ATP-binding cassette (ABC) superfamily, which includes P-glycoprotein (P-gp) or multidrug resistance protein 1 (MDR1), has been identified as the primary efflux transporter (Banks 2016). Several additional MDR proteins have been identified, including MRP1, MRP2, MRP4, and MRP5, and breast cancer-related protein (BRCP) (Uchida et al. 2011), which is regulated by P-gp.

12.8 Changes in the BBB in Pathological Conditions

A complex interdependent functioning of the BMECs, pericytes, astrocytes, and other NVU components is responsible for the protection of the brain. They together perform additional functions such as regulating permeability, blood flow, angiogenesis, neurogenesis, and so on. In pathological conditions, these interactions are highly disrupted, making the brain susceptible to serious injury. The components of the NVU are sensitive to the immunological responses upregulated in the disease state. These responses include the higher levels of pro-inflammatory cytokines such as IL-1ß, IL-6, TNF-α, and interferon-γ (IFN-γ). The other substances that disrupt the BBB integrity include ROS, free radicals, prostaglandins, histamines, intra- and extracellular ionic compounds, and infective agents such as bacteria, fungi, viruses, and other pathogens. These agents trigger neuroinflammation that leads to disruption of the physiology and functions of the BBB.

Neurodegenerative disease results in the loss of a protein called agrin, a part of the proteoglycans in the BMECs (Krol 2012). Matrix metalloproteinases (MMPs) degrade occluding, fibronectin, laminin, and heparan sulfate that compose the BBB. A change in pericyte number can affect the amount of claudin 5 occludin, resulting in the weakening of the tight and adherens junctions (Bell et al. 2010). These BBB composition changes due to changes in the proteins trigger neuroinflammation by activating the immune cells of the brain. A downstream result of these is the disruption of the transporters on the BBB such as GLUT1, LRP, LDLR, and so on in very specific areas of the brain where the injury is located. Neuroinflammation also upregulates the vascular cell adhesion molecule-1 (VCAM-1) that further enhances the immune cell movement toward the action (Reijerkerk et al. 2008; Floris et al. 2004), thus damaging the BBB. The heightened immune cell response in pathological conditions may also trigger the natural immunosuppression mechanism mediated by cells such as regulatory T-cells (T-reg) or the myeloid suppressor cells (MSCs). This, too, is detrimental to the integrity of the BBB (Moliné-Velázquez et al. 2011).

A better understanding of the BBB's composition and the processes underlying the transport of molecules through the BBB will aid in the development of more precise and targeted nanoparticles for the effective treatment of neurodegenerative diseases such as tumors, Alzheimer's disease, Parkinson's disease, and multiple sclerosis.

12.9 Employment of Nanotechnology for the Treatment of Alzheimer's Disease

Nanoparticles (NPs) are materials with a diameter between 1 and 100 nm. Organic and inorganic materials may be used to synthesize NPs. There are NPs that are often used as nanocarriers, owing to their superior properties such as increased water solubility, biocompatibility, and biodegradability. The majority of AD therapeutics have low bioavailability and are unable to cross the BBB. NPs are the best candidates for the delivery of brain drugs because they can improve the medication's bioavailability and half-life even at low doses. NPs also improve therapeutic effectiveness by increasing the target specificities by reducing acute tolerance (Zhang et al. 2008; Lu et al. 2014; Rauf et al. 2019). There are different kinds of nanoparticles employed in the studies of AD. The most common researched are liposomes, dendrimers, and polymer-based NPs. The present section of the chapter focuses on the role of NPs in different AD pathogenesis (Table 12.1 and Fig. 12.5).

12.9.1 Liposomes

Liposomes were first used as a carrier for nanoparticles in 1965 as liposomal NPs. Liposomes are spherical vesicles with a single or bilayered lipid membrane, an aqueous nucleus, and an aqueous exterior (Wechsler et al. 2019; Wei et al. 2015). Liposomes are amphiphilic because phospholipid molecules in lipid vesicles are amphiphilic. The remarkable fact is that not all nanoscale mixtures of lipids and phospholipids contain liposomes. Certain nanoscale combinations of phospholipids exhibit properties that are distinct from liposomal properties, in which liposomal NPs are found exclusively in vesicle spheres such as hexagonal, micellular, or cubic phases. Liposomes are extremely biodegradable, nontoxic, and non-immunogenic. Liposomal NPs have a thickness of approximately 10 nm–10 μm. Liposomes allowed the delivery of both hydrophilic and hydrophobic agents through their hydrophilic cores and hydrophobic membranes. The adaptable liposomal NP structure enables the loading of samples (siRNA, dye, etc.) or therapeutic agents, thereby facilitating BBB penetration (Vieira and Gamarra 2016; Hu et al. 2010; Leonor Pinzon-Daza et al. 2013).

Liposomes used to treat Alzheimer's disease were designed to specifically target A peptides, thus preventing plaque formation. Few studies have shown that liposomes containing phosphatidic acid and cardiolipin enhance in vitro interaction with A oligomers. Additionally, several experiments indicated that PEG-coated

Table 12.1 Summary of nanocarriers used for Alzheimer's disease

Nanoparticle	Modifications	Therapeutic agents	Model animals	Results
Liposome	PEG coating	Beta-amyloid monoclonal antibodies	Postmortem Alzheimer's disease brain samples	Significant binding of the liposomes to amyloid-beta monomers
	CPPs modification	Rivastigmine	Mouse brain microvascular endothelial cells model	Increased drug transport across the blood-brain barrier
Dendrimer	PAMAM dendrimers	*N*-acetyl-L-cysteine	Rabbit cerebral palsy model	Reduced neuroinflammation and oxidative stress
	Cysteine dendrimer	KLVFF peptide	Fibrillar samples	Disrupted amyloid-beta peptide aggregation
Polymeric	Polyabsorbate	Nerve growth factor	Mouse scopolamine-induced amnesia model	Increased nerve growth factor levels in the brain, as well as improved recognition and memory functions
	Polyabsorbate 80 coated PBCA	Anti-amyloid abs	Rat Alzheimer's disease model	Increased drug transport across the blood-brain barrier
	PEG-PLGA	Fibroblast growth factor	Rat Alzheimer's disease model	Increased brain levels of basic fibroblast growth factor and enhanced spatial learning and memory

liposomes were used to operate on monoclonal anti-A antibodies. Apart from liposomes binding to A deposition in postmortem Alzheimer's disease brain samples, significant liposome binding to A monomers has been observed in vitro (Canovi et al. 2011; Karthivashan et al. 2018). Natural compounds such as curcumin and quercetin have anti-inflammatory, antioxidant, and anticancer effects. These anti-inflammatory properties are used to treat and protect against Alzheimer's disease. Several studies on curcumin-loaded liposomes have shown anti-amyloidal activity to fibrillation of Aβ under in vitro conditions.

By contrast, intranasal administration of quercetin liposomes significantly reduced hippocampal neuronal degradation in a rat model of Alzheimer's disease. These results raise the prospect of liposomal delivery of naturally occurring compounds to treat Alzheimer's disease. As a result, liposomal NPs are an excellent candidate for use in AD pharmaceutical systems (Tiwari et al. 2014; Hamaguchi et al. 2010; Ansari et al. 2009).

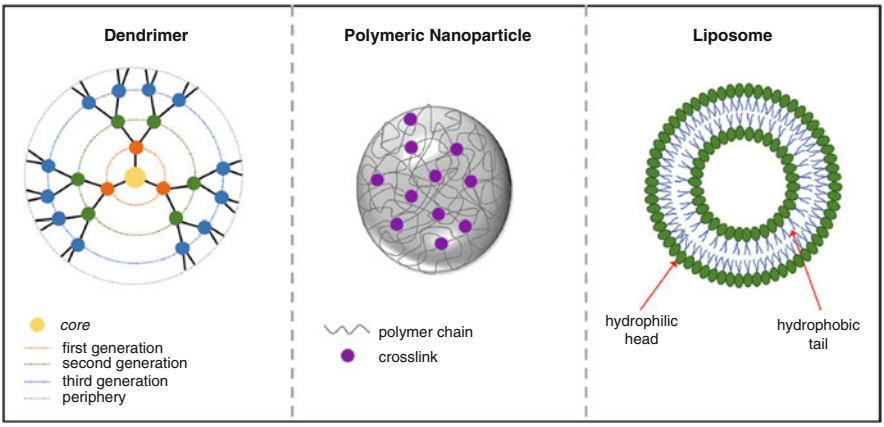

Fig. 12.5 Nanoparticles used to deliver treatment for Alzheimer's disease. Polymer nanoparticles, dendrimers, and liposomes are all examples of nanocarriers used to deliver therapeutic agents through the blood-brain barrier to treat Alzheimer's disease. The optimal particle diameter for crossing the blood-brain barrier has been determined to be between 5 and 200 nm. (Figure adapted from Wechsler et al. (2019))

12.9.2 Polymeric Nanoparticles

Polymeric nanoparticles measure between 1 and 1000 nm in size and are extremely flexible and tunable structures. Polymers have a particular combination of properties, which, unlike many other materials, enables them to be used in various drug delivery applications. These materials provide opportunities to monitor and modulate particle stability, loading performance, kinetic release, and surface modification ability (Pardridge 2007; Smith et al. 2016; Wohlfart et al. 2012; Chang et al. 2009; Ren et al. 2012). Polymers employed for the drug delivery system in the central nervous system include polysaccharides, poly(ethylenimines), poly(alkylcyanoacrylates), poly(methylidene malonates), and polyesters.

Polybutylcyanoacrylate (PBCA) was the first polymer-based nanoparticle to deliver the central nervous system with therapeutic compounds. The emulsion polymerization of polyalkylcyanoacrylate summarizes PBCA's nanoparticles. In this study, polysorbate 80-coated PBCA nanoparticles containing dalargin (an opioid peptide) were administered intravenously (Tween 80). The primary goal of this study was to achieve therapeutic amounts of dalargin in the central nervous system, which would illustrate the medicinal product's passage through the BBB. Subsequent studies discovered that when radioactive dalargin-loaded PBCA nanoparticles were used in the absence of polysorbate 80 coating nanoparticles, the amount of nanoparticles crossing the blood-brain barrier decreased. This and several other studies have shown that polysorbate 80 enhances the penetration of polymeric nanoparticles through the BBB (Begley 2004; Lockman et al. 2004; Kreuter et al. 2003; Schroeder et al. 1998; Das and Lin 2005).

In the bloodstream, nanoparticles are most readily collected through opsonization by the reticuloendothelial system. Reduced particle size and adsorption of surfactants (e.g., polysorbate 80) have been shown to benefit the residence time of nanoparticles in circulation. Adsorption of nanoparticles of the surfactant polysorbate 80 seemed to have been demonstrated in part by a decrease in nanoparticle removal by the reticuloendothelial network. Additionally, using small molecules and growth factors, PBCA nanoparticles coated with polysorbate 80 have been used to diagnose Alzheimer's disease. Rivastigmine is an acetylcholinesterase inhibitor that is currently being used to treat Alzheimer's disease. Previously published research demonstrated that rivastigmine-loaded PBCA nanoparticles coated in polysorbate 80 were superior to uncoated nanoparticles and free rivastigmine. In comparison to filled nanoparticles, PBCA-loaded rivastigmine nanoparticles coated with polysorbate 80 accumulated more readily in the brain than nanoparticles without coating or free rivastigmine. Additionally, the polysorbate 80 coating of the nanoparticles has been shown to minimize liver accumulation; administration of growth factors naturally found in the brain has also been shown to improve the pathophysiology of Alzheimer's disease in animal models as compared to uncoated nanoparticles (Khemariya and Khemariya 2016; Anand and Singh 2013; Bullock et al. 2005; Costantino et al. 2005).

Poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(lactic-co-glycolic acid) (PLGA) are all examples of polymer nanoparticles that are used to deliver pharmaceuticals into the central nervous system. These nanoparticles were designed for intranasal administration in order to circumvent the blood-brain barrier. Due to its large surface area, proximity to the brain, and high capillary density, an intranasal injection is an appropriate route of nanoparticle administration. The addition of PEG to the surface of PLGA further improved their ability to act as a carrier for drug delivery. Specifically, *Solanum tuberosum* lectin was used to selectively conjugate the PEGPLGA nanoparticles to the nasal epithelial membrane's *N*-acetylglucosamine for transmission to the brain. Intranasal administration of lectin-modified nanoparticles to rats with Alzheimer's disease resulted in a rise in basic fibroblast growth factor levels in the brain compared to control rats. Improvements in rats' spatial learning and memory abilities were observed (Loureiro et al. 2016; Sirelkhatim et al. 2015; Hanson and Frey 2008; Sánchez-López et al. 2018).

Utilization of organic, biodegradable, and biocompatible polysaccharides, such as chitosan, is one such example. Previously published research established the use of chitosan nanoparticles for the intranasal delivery of estradiol, resulting in increased estradiol levels in the central nervous system. However, systemic administration of chitosan nanoparticles was used to deliver amyloid peptides, dopamine, and caspase inhibitors to the central nervous system. In general, the ability of polymeric nanoparticles to cross the blood-brain barrier is highly dependent on surface modifications. The presence of surfactants or ligands causes the receptor to undergo endocytosis. These and many other considerations must be considered when developing nanoparticle-based drug delivery systems that cross the blood-brain barrier for the clinical treatment of Alzheimer's disease and other neurodegenerative diseases (Jia et al. 2016; Elnaggar et al. 2015; Wilson et al. 2010).

12.9.3 Dendrimers

Dendrimers have shown promise for diagnosing and treating neurodegenerative diseases. Dendrimers are complex three-dimensional polymers with tightly controlled mass, scale, form, and surface chemistry. Numerous technologies based on dendrimers have been developed to aid in the modification of dendrimers' suitability as drug delivery vehicles. This involves the possibility of maintaining therapeutically effective drug levels, increasing the distribution of active agents for a longer half-life, enhancing drug transport and stability, and improving medicinal efficacy (Costantino et al. 2005; Loureiro et al. 2016; Sirelkhatim et al. 2015). Additionally, the dendrimer surface versatility allows biomolecules to bind to internal cavities with strong drug-loading capacities. Dendrimers have been shown to bind to proteins, lipids, and nucleic acids with high affinity. Numerous dendrimers have been investigated for drug administration, imaging, and theranostics. This include the following: Due to their chemical properties, PAMAM dendrimers were one of the most extensively studied structures. This PAMAM dendrimer capability enables the carriers to be used in a wide range of applications. Dendrimers have been used to treat Alzheimer's disease as anti-amyloidogenic agents. For example, PPI maltose (PPI-G4-Mal) glycodendrimers of the fourth generation and PPI maltose (PPI-G5-Mal) glycodendrimers of the fifth generation have demonstrated the ability to disrupt the amyloid-(A) peptide's A(140) fibrillation. Each of these systems employs a unique mechanism to prevent A from fibrillating. While PPIG4-Mal forms clumped fibrils and high-value amorphous aggregates at low-dendrimer-peptide ratios, the fifth generation of fibril dendrimers prevents the formation of grain-based non-fibril amorphous aggregates. These studies demonstrate that preventing fibril clumping can be an effective way to slow the progression of Alzheimer's disease. The use of cationic phosphorus dendrimers has shown promise (CPD). To be more precise, CPDs (generation 3 and 4) demonstrated anti-inflammatory properties by preventing the inhibition of acetylcholine hydrolysis and exhibiting antioxidant properties. CPDs also shown that the right levels of acetylcholinesterase inhibitor therapy are not antagonistic when used in conjunction with traditional pharmacological treatments for Alzheimer's disease (Klajnert et al. 2006; Luo et al. 2002; Kalomiraki et al. 2016; Aliev et al. 2019; Wang et al. 2014).

Dendrimers were also used to transport antioxidants and anti-inflammatory medications through the blood-brain barrier. Although the combination of neuroinflammatory and oxidative stress is correlated with a variety of neurodegenerative disorders, not just Alzheimer's disease, it is worthwhile to investigate dendrimers' ability to deliver neurotherapeutics across the blood-brain barrier. Moscariello et al. conducted research on the neuroinflammatory properties of dendrimers (Moscariello et al. 2018; Agrahari et al. 2019). Kannan et al. used PAMAM dendrimers to deliver *N*-acetyl-L-cysteine, an antioxidant and anti-inflammatory agent. PAMAM dendrimers were paired with a streptavidin adapter in Moscariello et al.'s research to investigate their absorption mechanisms and transportation through the blood-brain barrier using in vitro vivo models (Moscariello et al. 2018; Menjoge et al. 2010) (Fig. 12.6).

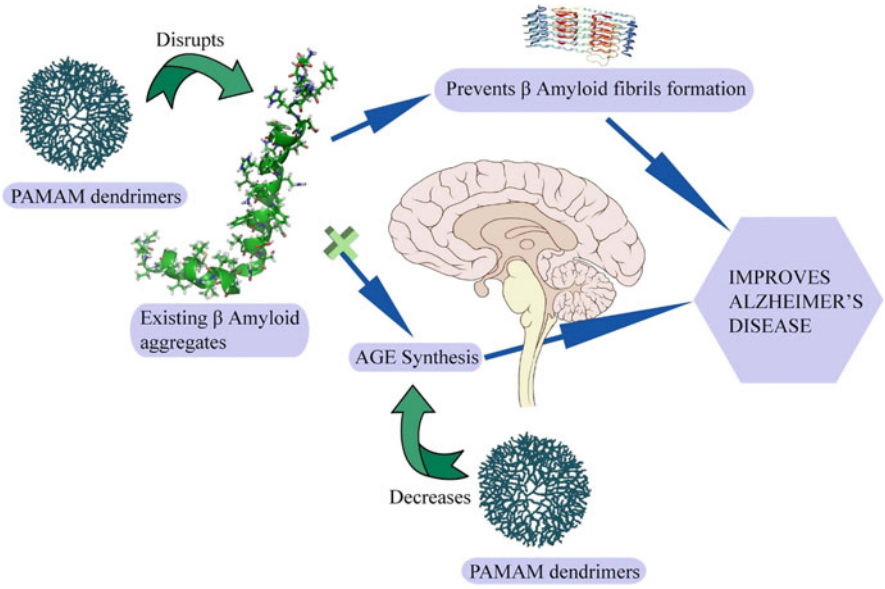

Fig. 12.6 Dendrimer-mediated delivery of drug for the disruption of beta amyloids. (Figure adapted from Harilal et al. (2019))

Dendrimers have also been used to gain a deeper understanding of the processes underlying Alzheimer's disease. Dendrimers were initially used to study the formation of amyloid plates, which is a characteristic of the onset and progression of Alzheimer's disease. For example, the KLVFF sequence, which is required for the formation of sheet structures, is one of the important peptide sequences involved in the formation of amyloid aggregates. Chafekar et al. formed a dendrimer scaffold that functions in KLVFF and inhibits aggregation A(142). Additionally, these constructions demonstrated the ability to disassemble preexisting amyloid. In sum, these results are important for a more complete understanding of tuned dendrimer chemistry and formulations for the effective diagnosis and treatment of Alzheimer's disease and other neurodegenerative diseases (Klajnert et al. 2006; Luo et al. 2002).

12.9.4 Gold Nanoparticles (GNPs)

GNPs have been extensively studied in several biomedical applications, including AD therapy, to deliver drugs and theranostics. A study by Kogan et al. employed GNPs to remove amyloid aggregates in a low microwave fields (Guerrero et al. 2010). GNPs dissolved aggregates of Aβ peptide and inhibited additional aggregations of Aβ peptide by producing local thermal energy (Guerrero et al. 2010). Another study by Liao et al. developed negative charged GNPs and showed that GNPs inhibited Aβ fibrillation and redirected Aβ into spherical oligomers and

fragmented fibril (Peng et al. 2014). Similar results were seen when GNPs were modified with a carboxyl group. In this effect, the negative surface potential of GNPs is significant. Prades et al. modified the GNPs with CLPFFD and THRPPMWSPVWP peptide sequence. They showed that due to the presence of transferrin receptor in the BBB endothelial cells, it leads to increased brain permeability under in vitro and in vivo conditions (Guerrero et al. 2010; Sivanesan and Rajeshkumar 2019).

12.10 Future Direction

Regarding AD treatment, notable studies demonstrating the importance of nanotechnological technologies for therapeutic delivery and AD theragnostic have been carried out. Nonetheless, most of the research is preclinically focused. The findings suggest that the clinical trials and nanotechnology-based treatment in AD will increase therapeutic outcomes shortly. Many new technologies and nanotechnology-based approaches have demonstrated promise in processing drug/biomolecules and/or imaging agents in the BBB for AD therapy. These nanotechnological strategies may help enhance the efficiency without problems of the NP-mediated CNS delivery.

12.11 Conclusion

Alzheimer's disease is a complex condition of progressive dementia that is very difficult to treat because of the impenetrable blood-brain barrier. Though it is disrupted in AD, it is still challenging for delivering drugs across BBB. Nanoparticles allow the design of clever therapeutic carriers, which can simultaneously cross the BBB and carry payloads to the specific targets. In addition, substantial research was carried out in nanoparticles that allowed for the brain's imaging to detect early biomarkers with high sensitivity in AD. Working in this field is promising but not sufficiently good to bring such technology in AD therapy from bench to bed. Several key aspects, including pharmacokinetics, metabolism, and toxicity issues, are still adequately addressed with many nanomaterials, mainly inorganic nanoparticles (significantly used in imaging studies). Finally, most nanoparticles examined for AD therapy demonstrated their action, mostly in preclinical studies.

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Role of Impaired ABC Transporters in Alzheimer's Disease

13

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Abstract

The ATP-binding cassette (ABC) superfamily groups are membrane proteins that serve as active efflux pumps for many substances, together with therapeutics. ABC transporters comprise of a highly conserved "cassette-like" domain that

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catalyzes the ATP hydrolysis providing the energy needed for the transport of substances against a concentration gradient. They actively transport both the endogenous and exogenous substances and implicated in the absorption, distribution, and excretion of several xenobiotics. They exhibit ubiquitous expression throughout the human body, with a special relevance in barrier tissues like the blood-brain barrier (BBB). At this level, they play a physiological role in tissue protection by reducing or limiting brain accumulation of neurotoxins. Furthermore, dysfunction of ABC transporters, at expression and/or activity level, has been associated with many diseases. Alzheimer's disease (AD) is a progressive neurodegenerative disease and the most common form of age-related dementia that starts with memory loss and progresses to include severe cognitive impairment. In recent years, it has been shown that inadequate Aβ, which are physiologically assisted by the superfamily ABC transporters at the brain barrier, are important in the imitation and the progression of the disease. This book chapter highlights the significance of this alternative approach as a novel in AD, to provide the researchers an opportunity to evaluate the potential aspects of ABC transporters in AD treatment.

Keywords

ATP-binding cassette transporters · Central nervous system · Alzheimer's disease

13.1 Introduction

ABC transporters are one of the main super families of transporter proteins (Thomas and Tampé 2020). ABC transporters are transmembrane proteins localized on cells as well as organelles and are extensively expressed in all organisms. In humans, ABC transporters are predominantly expressed in cancer cells as well as lipo-processing cells, for example, macrophages (Nedeljković et al. 2021). The ABC transporter family contains 48 genes (for humans) spanning the gene codes *abca* to *abcg*. The most common researched of these are P-glycoprotein or PGP (abcb1; MDRI), "breast cancer resistance protein" or BCRP (abcg2), as well as the "multi-drug resistance-associated proteins" or MRPs ($abcc_s$). These transporters are identified to exist at barriers between the blood and the CNS (Ek et al. 2010; Møllgård et al. 2017) as well as between the blood and CSF (Kratzer et al. 2013; Møllgård et al. 2017) and the CSF and the CNS. The superfamily of ATP-binding cassette (ABC) transporters controls drug distribution, metabolism, as well as bioavailability in cells and the extracellular matrix; the transporter thus plays a very significant role by limiting the accumulation of drug in the tissues, also with drug resistance (Linton 2007). At present, only few members are recognized as members of neural stem/progenitor cells as well (NSPC) (Broccardo et al. 2006; Mohan et al. 2006. The superfamily is composed of many transporters belonging among the seven subfamilies of ABC A and ABC G. In the blood-brain barrier (BBB), these subfamilies include ABCB subfamily consequent to P-glycoprotein

(P-gp) which mediates multidrug resistance (MDR), the subfamily ABCC of multidrug resistance-related proteins (MRP), and the subfamily ABCG (breast cancer resistance protein, BCRP (Leslie et al. 2005). The broad and partly overlapping specificity of substrate on several hydrophobic compounds is common to multidrug transporters. They are exclusively dispersed in organs with secretive or barrier functions, together with the intestine, renal, liver, and lungs, as well at the BBB and the choroid plexus, chiefly for neurodegenerative disease. They are categorized into the apical membrane faced with the luminal surface of the tubes, tubuli, and canaculi or to the basolateral membrane in epithelia or endothelium. This functionality and polarization at the cell membrane allow guided transport across these cellular obstacles (Leslie et al. 2005); therefore, ABC transporters help in fulfilling the important function in excreting various peptides and compounds. Such barrier plays a prominent role in linking the cellular-intracellular intra-compartment and intracellular environment with the systemic outer bloodstream, especially in diseases with compartmental organ associations. Because this role may also play a part in the pathophysiology of neurodegenerative disorders, the brain is considered one of the largest compartments surrounded by barriers. Over the past 10 years, the focus of a recent AD research area has been on blood-brain barrier transporters in the ATP-binding cassette (ABC) and in other CNS cells. In order to move substrates across the cells, tissues and organelle's membranes, ABC transporters utilities the ATP. There are different types of molecules, substances, compounds, and drugs which act as substrates for ABC transporters; among them are cholesterol, peptides, lipids, toxins, and certain groups of drugs; therefore, ABC transporters become very core part of many biochemical and physiological reactions in maintaining the homeostasis of the body by metabolism extrusion and restricting drug absorption. Researchers recently found that ABC transporters play an important role even in diseases, where pathways and processes involving ABC transporters are changed. For some types of ABC transporters with role in AD and CNS like BCRP, MRP1, P-gp, ABCA1, and ABCA2 are associated with high concentrations of Aβ brain levels. It is still unclear how, and if accurately, ABC transporters add to AD pathophysiology. This lack of comprehension offers new insights, particularly with the promise of untying disease data and identifying targets that could help develop new therapeutic strategies for AB. This lack of understanding provides the opportunity which is discussed in this chapter.

13.2 ABC Transporter Superfamily

The largest family of transmembrane protein represents the ABC genes. By binding to ATP, these proteins use energy all the way through the cell membrane for the purpose to drive the transport of different molecules (Dean and Allikmets 1995). Depending on the organization and sequence of their ATP-binding domains, proteins are designated as ABC transporters, known as nucleotide-binding folds (NBF). Generally, the functional protein comprises two NBFs and two domains of the transmembrane (TM). There are 6–11 membrane-spanning helices in the TM

domains which provide substrate specificity. In the cytoplasm, NBFs are located and transmit the energy to carry the substrate throughout the membrane. They are mainly involved in the importation of essential substances into bacteria that cannot be obtained via diffusion (e.g., carbohydrates, vitamins, metal ions, etc.). The shuttling of hydrophobic compounds either inside the cell as part of metabolic processes or outside the cell for transport to other organs, secretion from the body, is the major known function of eukaryotic ABC transporters. Eukaryotic ABC genes are organized either as full transporters or as half transporters containing two TMs and two NBFs. The latter has to form homodimers or heterodimers to act as functional transporter. In eukaryotic genomes, ABC transporters are widely diffused and highly conserved across the species, indicating that majority of these genes have been present since the eukaryotic origin. Depending on the similarities in gene structure (half versus complete transporters), domain order, and on sequence homology in the NBF and TM domains, the genes can be cut into subfamilies. Seven subfamilies of the mammalian ABC gene exist, five of which are found in the genome of *Saccharomyces cerevisiae*. One of the major superfamilies of proteins, which are well distributed in all animals, from prokaryotes to humans, is ATP-binding cassette transporters (ABC transporter). These proteins are categorized according to their ABC domains(s) sequence and organization (Pohl et al. 2005). In eukaryotes, the transporters of ABC are expressed in intracellular compartments such as plasma membrane, Golgi, endosomes, multivesicular bodies, endoplasmic reticulum, peroxisomes, and mitochondria (Dean and Annilo 2005). In humans, around 48 ABC transporters have been identified so far, divided according to their structural characteristics into seven families (called ABC A–G). ABC proteins are primarily involved in the transport of vitamins, lipids (i.e., cholesterol, phospholipids, glycolipids, etc.), bile salts, steroids, toxins, and medicine and metabolisms via biological membrane through molecular processes (Molday et al. 2009). Accumulating evidences support the fact that the subfamily-A of the ABC transporter has the key role in human physiology, and when mutated or altered, they cause different diseases (Peelman et al. 2003). Tangier (ABCA1), Alzheimer's (ABCA2/ABC7), Stargardt's (ABCR/ABCA4), and Harlequin ichthyosis (ABCA12) (Tarling et al. 2013) are examples of ABC A subfamily disorders.

13.2.1 ABCA (ABC1)

This subfamily contains 12 set of transporters that are classified into two subgroups based on their phylogenetic and intron structure. The first group consists of around seven genes dispersed on six chromosomes (ABCA1, ABCA2, ABCA3, ABCA4, ABCA7, ABCA12, and ABCA13), while in the second group, it contains only five genes (ABCA5, ABCA6, ABCA8, ABCA9, and ABCA10) located on chromosome 17q24 as a cluster. Some of the largest ABC genes are located in the ABCA subfamily, most of which are >2100 amino acids. The ABCA1 and ABCA4 (ABCR) proteins, only two members of this subfamily, have been thoroughly studied. As per the role of ABC1 protein, it is involved in cholesterol transport

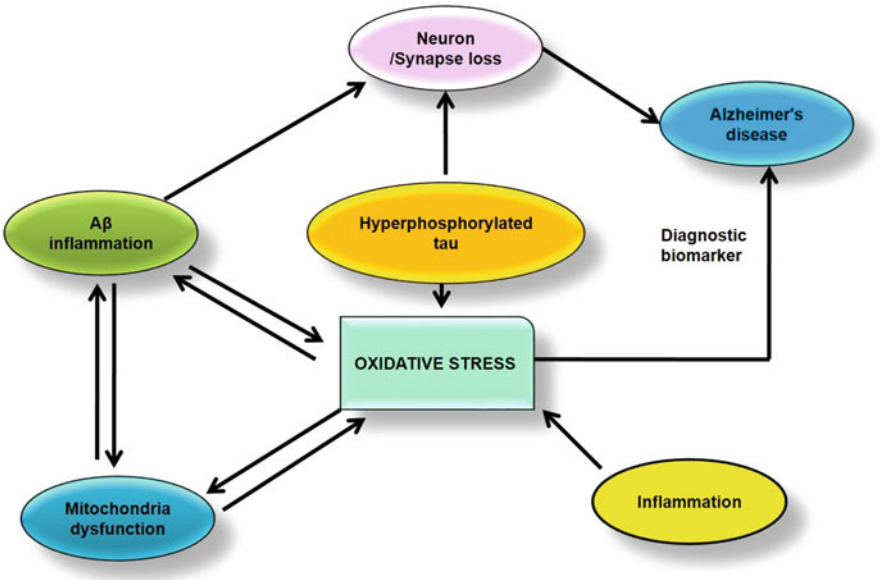

Fig. 13.1 Oxidative stress in Alzheimer's disease. The schematic diagram shows how oxidative stress can be induced by mitochondrial dysfunction, inflammation, hyperphosphorylated tau, and Aβ accumulation in AD

and high-density lipoprotein (HDL) biosynthesis disorders. In the outer segments of the photoreceptor cell, the ABCA4 protein is linked to the transport of vitamin A derivative and ultimately plays an important role in visual cycle (Fig. 13.1).

13.2.2 MDR/Tap (ABCB)

ABCB subfamily is one of the unique families as it includes both full and half transporters. As members of this subfamily, seven half and four full vans are currently listed. ABCB1 (MDR/PGY1) is one of the first human ABC transporters that has been cloned and characterized by its capability to present a phenotype of multidrug resistance to cancer cells. The blood-brain barrier and the liver include the functional sites of ABCB1. Proteins like ABCB4 and ABCD11 are excessively found in the liver in order to assist in bile secretion. ABCB2 and ABCB3(TAP) genes are among the half transporters that form a heterodimer in order to carry peptides introduced as antigens toward the ER. The ABCB9 half transporters are the closest homology of the TAPs which were localized to lysosomes. The remaining four half transporters are restricted in the mitochondria, ABCB6, ABCB6, ABCB8, and ABCB10, where they act in the metabolism of iron and the transport of precursors of Fe/S proteins.

13.2.3 ABCC (MRP/CFTR)

The next subfamily of ABCC generally comprises about 12 different transporters with huge functional range that includes cell surface receptors, ion transporter, and secretion of toxins. The protein CFTR is a type of ion chloride channel that has a major role nearly in the exocrine secretions, and cystic fibrosis is caused by mutations in CFTR (Quinton 1999). Proteins ABCC8 and ABCC9 bind to sulfonylurea and control the channels of potassium involved in insulin secretion modulation. Nine MRP-associated genes make up the majority of the subfamily. Of these, drug conjugates are transported into glutathione and other organic anions by ABCC1, ABCC2, and ABCC3. Proteins ABCCA4, ABCC5, ABCC11, and ABCC12 are very small in size than other genes, but similar to MRP1 and lack an amino-terminal domain that is not necessary for the purpose of transport (Bakos et al. 2000). Proteins ABCC4 and ABCC5 impart resistance, including PMEA and purine analogs, to nucleosides.

13.2.4 ALD (ABCD)

The human genome in the ABCD subfamily contains four genes, with two in the yeast and *Drosophila* genome, respectively. The yeast genome, PXA1 and PXA2 after dimerization forms a functional transporter and is incorporated in peroxisomes for oxidation of long chain fatty acids (Shani and Valle 1998). The half-transporters which can function as either homo- or heterodimers in the regulation of very-long-chain transport of fatty acids were encoded by all the genes.

13.2.5 ABCE (OABP) and GCN20 (ABCF)

The genes with an ATP-binding domain, such as ABCE and ABCF subfamilies, which are derived from ABC transporters, do not have a TM domain and are thought to be useful in membrane transport. The ABCE subfamily only contains oligo-adenylate binding protein, a substrate that recognizes oligo-adenylate which is formed in some viruses at the time of infection. This gene is present, but not in yeast, in multicellular eukaryotes, indicating that it is part of innate immunity. A pair of NBFs is included in each ABCF gene. The GCN20 cerevisiae gene promotes activation of eIF-2 kinase (Marton et al. 1997) and ribosome-associated human homolog, ABCFI, which is likely to have a similar function (Tyzack et al. 2000).

13.2.6 ABCG (White)

This subfamily ABCG is considered to consist of having six half transporters and NBF at the amino side and TM domain at the carboxyl side. The ABCGI mammalian gene is involved in the transport of cholesterol control (Klucken et al. 2000). Among

Table 13.1 Members of the ABC transporter family

Subfamily name	Former name	Members	Linked diseases in humans	Number of genes	Number of pseudogenes
ABCA	ABC1	ABCA1, AB, A3, A4, A5, A6, A7, A8, A9, A10, A12, A13	Tangier disease	12	5
ABCB	MDR	ABCB1, B2, B3, B4, B5, B6, B7, B8, B9, B10, B11	Bare lymphocyte syndrome	11	4
ABCC	MRP	ABCC1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13	Dubin-Johnson syndrome	13	2
ABCD	ALD	ABCD1, D2, D3, D4	Adrenoleukodystrophy	4	4
ABCE	OABP	ABCE1		1	2
ABCF	CGN20	ABCF1, F2, F3		3	2
ABCG	White	ABCG1, G2, G4, G5, G8	Sitosterolemia	5	2

the other different genes of ABCG are ABCG2, a gene involved in drug resistance; ABCG5 and ABCG8 which help in sterol transport both in the liver and intestine; ABCG3, a gene which has been found mostly in rodents; and lastly ABCG4 which is found to be expressed in the liver. There is no literature available that explains the roles of the last two genes (Table 13.1).

13.3 Role of ABC Transporters in CNS

13.3.1 ABC A Family

ABC A1, a member of the ABC A family, has been studied as the most common transporter in the CNS and has been detected in choroid plexus epithelial cells, microglia, brain capillary, neurons, and endothelial cells at the protein or molecular level. ABCA has also been found in the brain capillary endothelial and abluminal membrane in cell line TR-CSFB3 belonging to rats (Panzenboeck et al. 2002; Fujiyoshi et al. 2007). The other members of ABCA together with ABCA2–9 are also found in epithelial cells of choroid plexus neurons, microglia, capillary endothelial cells, oligodendrocytes, and astrocytes of the mouse, rat, and human brain at the protein or mRNA levels (Bhongsatiern et al. 2005; Kim et al. 2006; Gosselet et al. 2009). ABCA family transporters are involved in apolipoprotein-dependent cholesterol efflux, sterol homeostasis, and lipid metabolism (Gosselet et al. 2009).

The role of these transporters in the CNS is, however, little understood. ABCA1 is found to be upregulated by ethanol in a recent research discussing the impact of alcohol on the fetal brain in mouse astrocytes in vivo as well as in fetal human astrocytes (Guizzetti et al. 2007). Cholesterol plays an important role in brain growth. Ethanol caused an increase in cholesterol efflux and a significant reduction in the level of intracellular cholesterol and induced a disturbance in cholesterol homeostasis but did not impair cellular cholesterol synthesis. Alcohol has a deleterious effect on the fetus as ethanol disturbs cholesterol homeostasis which affects the development of the brain. Moreover, ABCA1 has been shown to contribute in apoE-dependent cholesterol efflux in neurons as well as brain capillary endothelial cells.

Consistent with this, cholesterol efflux from ABCA1-deficient mice has reduced in microglia and astrocytes, resulting in cellular cholesterol accumulation and reduced removal of apoE (Hirsch-Reinshagen et al. 2004). This is an important discovery in that decreased levels of lapidated apoE decrease the proteolytic breakdown of amyloids (Jiang et al. 2008) which raises the chances of Alzheimer's disease. This forms a potential correlation between Alzheimer's disease and ABCA1 (Wahrle et al. 2004).

13.3.2 ABC B Family

One of the best-studied transporters of the ABC B family in CNS is ABCB1 (P-glycoprotein, P-gp, and ABCB1/MDR1). Very few studies have been conducted on other ABC B members in the brain. mRNA for phosphatidylcholine transporters, ABCB4 (Pglycoprotein3, PGY3) and mitochondrial transporters, ABCB7, ABCB8, (MABC), ABCB10 (mitochondrial ABC transporter 2, MTABCT2 and ABCB6 (mitochondrial ABC transporters3, MTABC3) have been found in capillary endothelial cells of pigs, rats, cows, humans and mice. Additionally, ABCB4 as well as ABCB11 (BSEP, bile export pump) mRNA has been identified in the choroid plexus in humans and rats; the protein level of ABCB2–11 has not been observed in the CNS.

13.3.2.1 ABCB1 (P-Gp, MDRI, P-Glycoprotein)

13.3.2.1.1 ABCB1 Speech, Localization, and Function

Juliano and Ling in 1976 explained the phenomenon of drug resistance in tumors by discovering ABCB1 drug resistance cell line. In the normal barrier and also in excretory tissues like the liver and intestine, ABCB1 was observed to be physiologically expressed. In 1989, the ABCB1 protein was found to be present in the capillary endothelial cells of the human brain (Thiebaut et al. 1989; Cordon-Cardo et al. 1989). The mRNA, protein, as well as function of ABCB1 were recognized a few years later in cow, pig, rat, mouse, dogfish, and killifish capillaries of the brain, as well as the monkey, dog, and cat endothelial cells (Miller et al. 2002; Pekcec et al. 2011). It has become apparent over the last 15 years that ABCB1 plays a significant role in the operation of the blood-brain barrier. Four factors make ABCB1 a crucial

obstacle to the entry into the brain of a huge quantity of xenobiotics which include CNS drugs as well as toxins, expression, localization, potency, and multi-specificity (Begley 2004). Firstly, in brain capillary membranes, ABCB1 is strongly expressed. Studies have also reported considerably higher ABCB1 protein levels in plasma membranes sequestered from the capillaries of the brain of mice or rat in comparison to any other tissue tested for plasma membranes (Miller et al. 2008). Secondly, the localization of endothelial capillary cells is incessant with ABCB1 acting as a drug outflow pump as well as a blockade in the CNS for entry. There is a set of evidence relating to the acceptance of ABCB1 plasma membrane lumen (Roberts et al. 2008; Hartz et al. 2010a, b). On the other hand, it is still the role and degree of abluminal and intracellular ABCB1. Thirdly, the substances that prevented from crossing the endothelium capillary of the brain by ATP-driven efflux transport. In accordance with this, the findings of the in vivo laboratory indicated that loperamide, an ABCB1 substrate as well as an opioid that does not have central analgesic effects and also cannot traverse the blood-brain barrier, exert considerable antinociception when cyclosporine was first administered with ABCB1 inhibitor in mice. Fourthly, ABCB1 has a surprisingly wide range of substrate compounds with a large structure variety that ranges from tiny molecules, for example, loperamide (MW 285–477 Da) and verapamil and morphine for amyloid (MW4200 Da) (Kuhnke et al. 2007; Hartz et al. 2010a, b). Additionally, different groups of xenobiotics, for example, HIV protease inhibitors, antibiotics, opioids, chemotherapy, etc., can be controlled by ABCB1 (Bauer et al. 2005). CNS is shielded from potential destructive toxins by a perfect "gatekeeper," ABCB1 in the brain capillary endothelium. On the other hand, ABCB1 functions as a drug barrier. Two studies in the Netherlands from the Schinkel Laboratory best exemplify this "double-edged" sword feature of ABCB1. CNS-protective role of ABCB1 was first identified in ABCB1-deficient MDR-1 knockout mice with ivermectin, an anthelmintic drug as a standard parasite control measure. Although this is usually harmless technique and remained unaffected by wild type mice, all MDR-1 knockout mice died. Subsequent experiments showed that the absence of blood-brain barrier ABCB1 results in higher brain absorption for neurotoxic ivermectin, which usually cannot cross the endothelial brain capillary into the CNS. In vivo follow-up dosing experiment supported these results and showed an increase 5–50-fold inside the plasma to the brain; the proportion of drugs which are substrates, in addition, do not pass the brain in MDR1-knockout mice (Schinkel et al. 1996). The physiological significance of ABCB1 in shielding the brain and the difficulty of delivering therapeutic drugs into the CNS is illustrated in these examples. Whereas the most information presented on the ABCB1 in the CNS is from the endothelial cells of brain capillary, the mRNA, protein, and functional levels of ABCB1 are also expressed in other human brain cells (Daood et al. 2008) and monkey, sheep (Bougoin et al. 2008), rat (Niehof and Borlak 2009), and mouse cells (Wu et al. 2009). The location of the transporter was in the cytoplasmic vesicles as well as the plasma membrane as revealed by electron microscopy in pericytes from human brain sections (Bendayan et al. 2006). There

were no recorded functional studies of ABCB1 in pericytes. ABCB1 is found inside the astrocytes in the caveolae, nuclear envelope plasma membrane, astrocytic foot, and coated vesicles. It has also been suggested to play a role in the nucleotide's efflux (Ronaldson et al. 2004; Wu et al. 2009). MLS-9 cell line of rat microglia also contains ABCB1 located along the nuclear envelope as well as the plasma membrane (Ballerini et al. 2005). Functional tests of ABCB1 in this cell line revealed efflux of saquinavir, indinavir, and HIV protease from cell (Scott Kim et al. 2009). The expression of ABCB1 has been observed in the plasma membrane of progenitor cells as well as neural stem cells of the human fetus (Daood et al. 2008). More tests of ABCB1 in the choroid plexus have been performed. ABCB1 transport of 99mTc-sestamibi from human, rat, and mouse intact choroid plexus tissue indicates apical localization and transport of substrate to cerebrospinal fluid. In isolated choroid plexus epithelial cells of sheep, the expression of ABCB1 protein was expressed (Bougoin et al. 2008). In comparison, the experiments in the choroid plexus epithelial cell of pig as well as rat experiments showed the localization of ABCB1 in the sub-apical vesicles; in these studies, transport via ABCB1 was not spotted (Daood et al. 2008; Niehof and Borlak 2009).

13.3.2.1.2 Control on ABCB1

ABCB1 regulation has been observed mainly in endothelial cells of brain capillary as well as to a smaller extent in the choroid plexus in the CNS and astrocytes. During the last 5 years, many pathways of signaling have been mapped that control ABCB1 in the brain. Here, we briefly summarize the findings of inflammatory mediators, oxidative stress, and nuclear receptors on ABCB1 control.

13.3.2.1.3 Control of ABCB1 in Inflammation

The first regulatory study conducted on ABCB1 regarding endothelial capillary cells of the brain dealt with the cause of transporter inflammation. In a research, the exposure of low levels of ET-1, TNF-alpha, or LPS to isolated brain capillaries of rats (Hartz et al. 2006; Bauer et al. 2007) resulted in a reversible and fast decrease in transport activity of ABCB1 but the expression of the protein showed no improvement (Hartz et al. 2004). Binding of ligand to the TLR4, TNF-R1, ETB, TNF-R1, and TLR4 receptors and activation of PKC and NOS were involved in the signaling process, resulting in rapid membrane recovery of ABCB1 and a decrease in ABCB1-mediated transport (Hartz et al. 2006). For a longer time frame (hours), exposure of ET-1 or TNF-α to the brain capillaries for a longer period of time has increased the expression as well as transport activity of ABCB1 proteins (Bauer et al. 2007). Such a continuing consequence was facilitated by a similar signaling mechanism like the abovementioned short-term effect. The other studies based on in vitro cultures of capillary endothelial cells in the pig or human brain, higher levels of mRNA and ABCB1 protein were subsequently found by the treatment with TNF (Poller et al. 2010), but the function of ABCB1 showed no effect. On the other hand, IL-1 and IL-6 have decreased ABCB1 mRNA and protein, respectively (Poller et al. 2010). The conflicting results were also produced through in vivo studies. Seelbach et al.

(2007) in a study conducted on a rat model of peripheral inflammation and higher expression protein ABCB1 inside the brain capillaries found a decreased brain uptake of morphine as well as ABCB1 substrate, and, in addition, decreased morphine antinociception was observed, suggesting that the overexpression of ABCB1 excluded morphine from the brain. Goralski et al. (2003) found intraventricular LPS injection-facilitated brain inflammation decreased overall brain ABCB1 mRNA expression in rats, and ABCB1 substrate digoxin mRNA increased brain absorption.

In in vitro cultures of rat astrocytes, ABCB1 protein expression was increased by TNF-α and IL-1β, while gp 120 and IL-6, an envelope glycoprotein of HI virus has resulted in decrease in ABCB1 expression. The transport efficacy was also decreased by IL-6, and gp120 (Ronaldson and Bendayan 2006). Another study showed upregulation of ABCB1 protein by CT1, IFN- γ, CNTF, IL-6, and LIF while working on mouse astrocyte cell cultures and CNT-knockout mice, based on CNTF effect (Monville et al. 2002). The other variation seen in these findings can be elucidated via the concept that the inflammation is a multifaceted phenomenon, and the inflammation response is dependent on model, context, time, and also dose. Even so, based on these studies, it is obvious that the moderators of inflammation have an intense reaction to ABCB1 in the brain. The exact mechanism is accountable for transport switches to be illuminated.

13.3.2.1.4 Regulation of ABCB1 by Oxidative Stress

Oxidative stress like ROS (reactive oxygen species), and CNS inflammation are linked to various CNS disease, for example, multiple sclerosis, brain tumors stroke, epilepsy, brain trauma, multiple, Alzheimer's as well as Parkinson's disease. ABCB1 mRNA along the vincristine transport as well as protein expression is increased during the in vitro exposure of endothelial cells of rat brain capillary with hydrogen peroxide for about 24–48 h (Felix and Barrand 2002). Hydrogen mediates signaling via NF-kB, PKC, c-jun, Akt, and ERK 1/2 which switched on ABCB1 transcription (Nwaozuzu et al. 2003). In vitro exhaustion of GSH in rat brain endothelial cells is associated with increased ABCB1 mRNA in addition to the expression of proteins; however, N-acetylcysteine, a ROS scavenger, eliminated this effect (Hong et al. 2006). These studies suggest an adequate sense of balance among cellular ROS and GSH, and the exhaustion of GSH has increased ROS, resulting in an increased ABCB1. In addition, these results may be significant in stroke research, as most of these signals have been seen in animal stroke models as well. On one side of CNS disease, it is obvious that the toxins and pollutants can also lead to the generation and production of ROS. In this concern, excess expression of isolated rat brain capillaries exposed to diesel particles which act as one of the environmental pollutants leads to the expression of ABCB1 protein and transport activity with the help of NADPH oxidase, a membrane linked enzyme complex that produces superoxide (Hartz et al. 2008). The increased oxidative leads to the TNF-α also TNF-R1 and c-jun signaling. These data include the involvement of environmental toxins in CNS disease.

13.3.2.1.5 Regulation of ABCB1 by Nuclear Receptors

The nuclear receptors function as transcription factors by binding to their ligands and cause their target genes to be transcribed. Some of the nuclear receptors, like aryl hydrocarbon receptor (AhR), PXR (pregnane X receptor), or CAR (constitutive androstane receptor), are activated by drugs as well as regulate ABC transporter transcription which comprises ABCC1, ABCC2, and ABCC3 apart from metabolizing enzymes (Geick et al. 2001). These nuclear receptors have clinical importance as well, because they can affect the pharmacokinetics of many drugs. We detected mRNA of PXR and protein expression in brain capillaries of pigs, rats, and mice; it was found that the activated PXR along with hyperforin, PCN, dexamethanose, or hyperforin has improved the expression of ABCB1 protein as well as transport action (Ott et al. 2009). Narang et al. (2008) have demonstrated that the dexamethasone-induced induction of ABCB1 is expected to be involved in the glucocorticoid receptor in endothelial cells of the rat brain capillary. In transgenic mice, the expressed human PXR have shown the upregulation of ABCB1, which has reduced the antinociceptive impact of methadone, a kind of CNS-active opioid, and ABCB1 substrate resulting in PXR activation of ABCB1, in the blood-brain barrier, has potential entailment for the release of CNS drugs (Theodoulou et al. 2006).

In this regard, treatment of HIV by means of a protease inhibitor is considered in which concentration of virus in the periphery is effectively lowered beneath the limits of detection; however, a load of virus in the brain is unchanged as the entry of protease inhibitor in the brain is restricted by ABCB1 and, therefore, changes the CNS as a store for HIV virus. To make matters worse, PXR ligands operate as protease inhibitors and may cause ABCB1 to contract even more, creating a barrier to HIV treatment in the CNS (Perloff et al. 2007). ABC transporters controlled by the nuclear receptors are still there situated within the human blood-brain barrier. Dauchy et al. (2008) revealed the expression of mRNA, of CAR (constitutive androstane receptor), PXR, AhR (aryl hydrocarbon receptor) of brain microvessels extracted from human brain biopsies. This regulatory system in the brain's capillary endothelium gets activated by and regulates ABC entry for transporters and may have significant medical consequences for CNS pharmacotherapy.

13.3.3 ABC C Family

There are 13 members of the ABC C family; out of these 13, 9 are transporters (ABCC1–6 and ABCC10–12); among them, information on ABCC12 in CNS is not available. Also ABCC6 and ABCC10 were detected in the CNS at the mRNA stage only. Specifically, ABCC6 (MRP6) mRNA was contained in capillaries of the bovine brain and endothelial cell cultures of humans, cows, pigs, rats, and mouse (Warren et al. 2009), microglia cell cultures of rats, and whole choroid plexus tissue cultures of humans and rats (Berezowski et al. 2004). In bovine brain capillary endothelial cell cultures, the mRNA of ABCC10 (MRP7) has been identified (Warren et al. 2009); on the other hand, the mRNA of ABCC1 (MRP8) has been

identified as well as protein in the neurons of the human brain sections (Bortfeld et al. 2000).

13.3.3.1 ABCC1

13.3.3.1.1 Function, Expression, and Localization of ABCC1

In 1992, Cole et al. first discovered ABCC1 in human cell H69AR. The presence of ABCC1 in CNS was first of all reported by Regina et al. in 1998. The authors showed in vitro mRNA and protein expression as well as transport function of ABCC1 in microvessel endothelial rat brain cell cultures. Later pig, human, mouse, cow, and rat endothelial cell cultures have shown the mRNA and protein expressions of ABCC1 (Ohtsuki et al. 2007; Roberts et al. 2008; Warren et al. 2009). At the blood-brain barrier level, the localization of ABCC1 is debatable. Although few reports showed ABCC1 expression in the albuminal membrane of capillaries of pieces of mouse brain (Kilic et al. 2008; Soontornmalai et al. 2006), apical localization of ABCC1 is seen in capillary endothelial cell cultures of the bovine brain and capillaries of sections of the human brain in other reports (Zhang et al. 2004; Nies et al. 2004). Roberts et al. (2008) in a recent study involving rat brain capillary immune stained isolates determined the location of ABCC1 which is predominantly in the abluminal membrane; however, a low level of the transporter is present in the luminal membrane as well. It's also questionable if data from functional studies can be used to evaluate the ABCC1 function. Through brain perfusion studies, it has been shown there are no differences in the ABCC1 substrate and 17 β-estradiol-D-17-β-glucuronide uptake in the brain in case of wild type in contrast to ABCC1 knockout mice, demonstrating that ABCC1 is non-operational or is present or absent in the case of luminal membrane (Cisternino et al. 2003).

For experiments involving wild type and ABCC1 knockout mice, intracerebral microinjection of 17-estradiol ID-17—glucuronide drastically reduced efflux in the brain of mice lacking ABCC1. This indicates that the endothelial capillaries contain functioning ABCC1 in the lumen of the membrane. From these observations, localization of ABCC1 in brain capillaries is uncertain and could depend on model, species, and study. Provided LTC4 is transported by ABCC1in both luminal and abluminal, it can possibly be localized considering that the boundary between the blood and the brain is the brain capillary endothelium responsible for communication in both directions, such as in inflammation. ABCC1 expression, as well as function, is well-known in choroid plexus, astrocytes, and microglia (Poller et al. 2010). ABCC1 mRNA and protein were found in astrocytes of rat brain compartments (Mercier et al. 2004), in rat astrocyte culture (Chen et al. 2009), astrocytoma cultures of humans (Spiegl-Kreinecker et al. 2002), and also astrocytes of human brain parts (Zhou et al. 2001). The transport function in astrocytes cultures of the rat was recognized, where the GSH release was induced by ABCC1 from cells in the way of oxidative stress (Hirrlinger et al. 2001, 2002). In other studies involving the cultured astrocytes of ABCC1 knockout mice as well as wild-type mice, ABCC1 is totally responsible and accounts for 60% of GSH export (Minich et al. 2006). The ABCC1 protein and mRNA have been detected in primary

microglia rat cell cultures as well as in MLS-9 microglia rat cell line (Dallas et al. 2003; Hirrlinger et al. 2002); apart from this, ABCC1 localization was also found in plasma membrane (Dallas et al. 2004). Furthermore, in rat, mouse and human choroid plexus tissues, ABCC1 protein and mRNA have been highly expressed (Gazzin et al. 2008; Saito et al. 2001) in Z310 and TR-CSFB (Hosoya et al. 2004; Shi et al. 2008). The rat and mouse choroid plexus studies have shown the localization of ABCC1 in the basolateral compartment (Sugiyama et al. 1999; Soontornmalai et al. 2006). With consistent localization in basolateral compartment, the choroid plexus transport was mediated by ABCC1 directly to the blood from epithelium of choroid plexus (de Lange 2004; Kusuhara and Sugiyama 2004). In addition to that, ABCC1 protein and mRNA were found to be also in bovine pericyte cultures in addition to pericyte isolated from rat brain (Berezowski et al. 2004; Shimizu et al. 2008), in nerve cell from human brain, as well as from the oligodendrocytes of rat cultures (Daood et al. 2008; Hirrlinger et al. 2002). Useful studies in these cells for ABCC1 have not been conducted yet.

13.3.3.1.2 Regulation of ABCC1

Some signaling mechanisms associated with ABCC1 in the CNS have been identified. The most excellent ones are the pathways that address the impact of HIV in the neurovascular unit transporters. In this sense, protein expression in addition to transport activity of ABCB1 and ABCC1 has shown to be increased in bovine capillary endothelial cells and in astrocyte cultures of rat and mouse by HIV proteins tat and gp120 (Hayashi et al. 2006; Ronaldson and Bendayan 2008). Inflammatory component in signaling involves NF-kB, TNF α, JNK, and MAPK. These findings are important considering that HIV virus is reserved in microglia and the CNS; astroglia are one of the main cellular targets of the virus inside the CNS. The other pathways of ABCC1 regulation have been set in the primary mouse astrocyte cell line (Ronaldson et al. 2010). The unconjugated bilirubin has shown to increase ABCC1 and facilitates its trafficking to the plasma membrane from the golgi apparatus (Hayashi et al. 2005). This leads to the protective mechanism where bilirubin is increased in disease states like hepatitis, selfprotecting its own toxicity. The mechanism by which bilirubin increases ABCC1 is uncertain, but a possible explanation is the activation of nuclear receptors.

13.3.3.2 ABCC2 (Associated Protein 2 or Multidrug Resistance, MRP2)

13.3.3.2.1 ABCC2: Localization, Expression, and Function

Detection of ABCC2 in 1996 by Paulusma et al. in rat hepatocytes resulted in a debate about expression of ABCC2 in the blood-brain barrier (Paulusma et al. 1996). In a study, Miller et al. (2000), immunolocalised ABCC2 to the luminal plasma membrane of brain capillaries of killifish, rat and pig (Jetté and Béliveau 1993). From the findings, there was no immunoreactivity reported in brain capillaries among TRcontrolled rats which are devoid of ABCC2 (Jetté and Béliveau 1993).

In comparison, different other groups could not notice ABCC2 protein or mRNA in brain capillary endothelial cultures, in samples of brain capillaries, and in total

brain samples of human, mouse, cow, or rat (Zhang et al. 2000; Sugiyama et al. 2003). From these observations, ABCC2 signal was absent in Western blot results carried out in whole-brain homogenate, brain capillary lysates, and even capillary-depleted brain homogenate in rats (Zhang et al. 2004; Johnson et al. 2006). ABCC2 is, however, an integral protein of the plasma membrane. ABCC2 protein was merely present in enriched plasma membrane from isolated brain capillaries of mouse and rat, and immunoreactive ABCC2 was found in isolated capillaries of the luminal membrane transported by ABCC2 (Bauer et al. 2008). By using ABCC2-null TR-control rats, these results were experimentally verified. According to Soontornmalai et al., the inconsistency about blood brain barrier expression of ABCC2 in different studies is because of species in addition to strain differences (Soontornmalai et al. 2006). Furthermore, ABCC2 mRNA, endothelial brain capillaries, and also protein expression have been monitored in rat and mouse choroid plexus (Choudhuri et al. 2003). ABCC2 localization in the choroid plexus has been confirmed as yet, but functional research on ABCC2 is missing. ABCC2 has not been studied in any other brain cells.

13.3.3.2.2 Regulation of ABCC2

Regarding the regulation of ABCC2, near the blood-brain barrier, only two studies have been conducted. In one study, there has been higher ABCC2 protein expression and transport rate in case of rat brain capillaries following PCN as well as dexamethasone exposure in vitro and in vivo (Bauer et al. 2008). Narang et al. (2008) demonstrated upregulation of ABCC2 mRNA as well as protein via dexamethasone in the next study, with cultured rat brain endothelial capillary cells by a way that is independent from GR activation (Narang et al. 2008). There are no other studies conducted or even published related to the ABCC2 regulation in the CNS.

13.3.3.3 ABCC3 (Multidrug-Associated Protein 3 Resistance, MRP3)

Concerning ABCC3 in the CNS, there is very less literature available. The mRNA expression of ABCC3 has been seen in rat, pig, human, as well as mouse brain capillary endothelial cell cultures, (Warren et al. 2009) in cultured rat astrocytes, microglia, and neurons, of choroid plexus tissues of rat as well as in humans (Niehof and Borlak 2009; Choudhuri et al. 2003). In immunostained brain capillaries of human brain parts and in choroid plexus of mouse, the ABCC3 protein has also been detected (Niehof and Borlak 2009; Soontornmalai et al. 2006). In human brain capillary endothelial cell line, hCME/D33, the transport of methotrexate by ABCC3 was found (Poller et al. 2008). The regulation of ABCC3 in the CNS has not been published yet.

13.3.3.4 ABCC4 (Multidrug-Associated Protein 4 Resistance, MRP4)

ABCC4 is one of the new family members of multidrug resistance-associated protein and is structurally very much similar to the ABCB1 in contrast to other ABC C family transporters (Belinsky et al. 1998). For the very first time, Leggas et al. have found the ABCC4 protein expression of ABCC4 of mouse cerebral vasculature brain parts and confined the transporter at the luminal membrane of the brain capillaries

(Leggas et al. 2004). These types of results were confirmed by studies carried on human, rat, and cow brain capillaries apart from the cell cultures of brain endothelial capillaries (Roberts et al. 2008; Ohtsuki et al. 2007). The localization of ABCC4 was described by Zhang et al. in luminal as well as in abluminal membrane of bovine brain capillary in endothelial cell cultures along with brain capillaries of rat (Zhang et al. 2000, 2004). There are no studies conducted and published on the transport activity of ABCC4 in the brain capillary endothelium or in endothelial cells of capillary. However, ABCC4 has proved to assist efflux transport of nucleoside analogs, organic ions, sulfate, and glutathione glucuronate-conjugated drugs, and prostaglandins (Zhou et al. 2008). Moreover, thiopurines, methotrexate, and topotecan are transported by ABCC4 (Adachi et al. 2002; Chen et al. 2002) proving that ABCC4 can perhaps assist blood-brain function in the blood-brain barrier by protecting the brain from xenobiotics as well as inducing resistance to some therapeutic drugs. On the other hand, the significance of ABCC4 on efflux transport toward the brain-blood barrier is not clear. The mRNA of ABCC4 is expressed in human and as well as in rat choroid plexus (Niehof and Borlak 2009; Choudhuri et al. 2003) but the protein expression of ABCC4 was observed only in the choroid plexus of the rat (Roberts et al. 2008). Studies conducted on rat and mouse choroid plexus have shown that the ABCC4 is localized in the choroid plexus epithelium basolateral membrane (Roberts et al. 2008; Leggas et al. 2004). In line with this, experiments showed the restriction of topotecan penetration by ABCC4 via choroid plexus epithelium into the cerebrospinal fluid in wild as well as knockout mice, suggesting protective role of ABCC4 (Leggas et al. 2004). Lastly, in other brain cells, the expression of ABCC4 has also been seen. The ABCC4 protein was also found in some parts of human brain astrocytes (Nies et al. 2004), and in rat astrocyte cell cultures, the ABCC4 mRNA was found there (Hirrlinger et al. 2002; Ballerini et al. 2002). In addition to this, the ABCC4 mRNA and its protein were found in rat microglia cell cultures (Ballerini et al. 2005; Dallas et al. 2004), but in rat nerve cell cultures, there was only ABCC4 mRNA and no protein (Hirrlinger et al. 2002). There are no studies available relating about the function of ABCC4 together with microglia, astrocytes, and neurons.

13.3.3.5 ABCC5 (or MRP5)

ABCC5 is mostly placed near the blood-brain barrier in the CNS and has been found as expressed at the mRNA degree in cow, pig, rat, mouse, and human brain cultured capillaries or endothelial brain cell capillaries (Wijnholds 1999; Zhang et al. 2000). ABCC5 has been located in the brain capillaries of mouse, where it was observed to be localized in the lumen of plasma membrane (Soontornmalai et al. 2006). The ABCC5 has been demonstrated in human brain capillaries as well as in bovine capillary endothelial cell cultures (Zhang et al. 2004; Nies et al. 2004). In the endothelial cell line hCME/D3 of human brain capillaries, the transport of methotrexate was confirmed via ABCC5 (Poller et al. 2008); extra functional studies on the blood-brain barrier of ABCC5 have not been carried out. In rat astrocyte cultures, ABCC5 mRNA has been extensively found; in addition to that, ABCC5 protein and mRNA were also observed in astrocytes of human brain slices and microglia of

cultured rats (Calatozzolo et al. 2005; Dallas et al. 2004). The mRNA of ABCC5 has been observed in rat nerve cells (Hirrlinger et al. 2002), and ABCC5 protein expression has been detected in the nerve cells of human brain slices (Nies et al. 2004). The mRNA of ABCC5 has been detected in choroid plexus of rat and humans, in addition to cultured rat oligodendrocytes (Niehof and Borlak 2009; Choudhuri et al. 2003). At present, the transport function of ABCC5 has not been identified in CNS cells.

13.3.4 ABCD Family

The family of ABCD transporters has been found in the peroxisomal membrane, where the metabolic breakdown of fatty acids, for the purpose of transport in peroxisomes, takes place (Theodoulou et al. 2006). ABC D is in charge of transporting fatty acyl-CoAs and long-chain fatty acids in this regard (Cartier et al. 1995). As a half transporter, ABCD1 gets dimerized with ABCD2 or even 3 so as to form a complete as well as functional active transport protein transporter, because it is a half-transporter (Liu et al. 1999). Protein and mRNA of ABCD1 have been found in endothelial cells of mouse brain capillary (Berger et al. 1999) as well as astrocytes, oligodendrocytes, and microglia both from the mouse brain and postmortem fractions of human brain (protein (Fouquet et al. 1997). The mRNA of ABCD-4 has been detected in mouse brain endothelial cells (Berger et al. 1999). In pericytes, neurons, and choroid, there is no information available about ABCD transport expression. The mutational defects of ABD1 gene in CNS have been found as the main reason of adrenoleukodystrophy, one of the lethal demyelinating recessive diseases in the CNS which is inherited progressively (Aubourg et al. 1993). Because of ABCD1 mutational defects, only few or no functioning protein transporting long chain fatty acids in peroxisomes for metabolic degradation are available. This enhances fatty acid accumulation in different body parts, especially in the white matter of the brain, where fatty acid breaks down the blood-brain barrier as well as resulting in a progressive destabilization of the axon myelin sheaths, which ultimately leads to severe injury to the brain and finally death (Kumar et al. 2008; Moser et al. 1995).

13.3.5 ABCG Family

ABCG1 (White1), ABCG4 (White 2), ABCG5 (White-3, sterolin-1) and ABCG8 (sterolin-2) are cholesterol and sterol transporters and responsible for the sterol as well as cholesterol homeostasis (Wang et al. 2008). In CNS, ABCG1 has been responsible in bovine brain capillary endothelial cells (mRNA, (Gosselet et al. 2009), astrocytes of the primary cell cultures of the mouse (mRNA, protein (Tarr and Edwards 2008), in neuron cultures of humans (mRNA), in mouse brain parts of nerve cells (Wang et al. 2008), in rat choroid plexus epithelial cell line,TR-CSFG3 (protein, (Fujiyoshi et al. 2007), in the whole choroid plexus of rat (mRNA),

(Fujiyoshi et al. 2007),where it is found to be present in the cell membrane (Fujiyoshi et al. 2007). ABCG4 has also been found in choroid plexus of rat (mRNA) (Wang et al. 2008). ABCG5 and ABCG8 have been found in tissues of rat choroid plexus. Further, other relevant studies have demonstrated that the brain uptake of plant sterols was highly increased in mice deficient of ABCG5 or ABCG8 (Cronican et al. 2010), demonstrating the presence of these two transporters inside the lumen of brain capillary endothelium. There are no other sources of information presently available to support these findings.

13.3.5.1 ABCG2 (Breast Cancer Resistance Protein, BCRP)

13.3.5.1.1 ABCG2 Expression, Localization, and Function

The ABCCG2 transporter has been discovered in human breast cancer cell line MFC-7 in 1998 by Doyle et al. with increased mitoxantrone resistance, but negative for both ABCB1 and ABCC transporters (Doyle et al. 1998). In the CNS, the expression of ABCG2 has been observed in stem cells (protein, (Islam et al. 2005), MLS-9 cell line of microglia (Lee et al. 2007), primary cultures of astrocyte (protein, mRNA) (Lee et al. 2007), in pericyte cell line (protein, (Shimizu et al. 2008) as well as in progenitor human cultures. The ABCG2 has been localized in the plasma membrane of human neural stem cells, where it has shown to promote the transport of prazosin indicating that neural stem cells are shielded by ABCG2 from xenobiotic insults (Islam et al. 2005). However, at the brain barrier, maximum analysis on ABCG2 in the CNS was carried out. By conducting differential screening of subtracted cDNA library in 2002, Eiseblatter et al. discovered ABCG2 at the blood-brain barrier and have found 2.1 kb of mRNA overexpression in porcine brain capillary endothelial cells treated with hydrocortisone (Eisenblätter and Galla 2002). By Northern blot technique, it was found that this type of mRNA was extensively present in endothelial cells isolated from pig brain capillaries. This encodes 656 amino acid proteins from ABC transporter that is largely similar to mouse and human ABCG2. Cooray et al. reported mRNA as well as protein expression of ABCG2 in microvessels from parts of the human brain shortly after this study (Cooray et al. 2002). ABCG2 protein and mRNA have also been found in cultured capillary endothelial cells, brain slices, or brain capillaries from mouse, rat, and cow (Lee et al. 2007; Hartz et al. 2010a, b; Aronica et al. 2005). The two main ABC transporters were identified by Dauchy et al., and they demonstrated that the ABCB1 and ABCG2 were extensively expressed in brain capillaries of isolated human biopsies, with a 20–25 times enhancement of each transporter in capillaries versus mRNA-based cortex as well as protein levels. As per ABCG2 blood-brain barrier tests, its localization was expressed in the luminal membrane of human and rat capillaries or endothelial cell cultures (Eisenblätter et al. 2003; Hori et al. 2004). Further, the functional studies conducted in endothelial capillary cell cultures of pig brain have revealed the efflux transport of daunorubicin (Eisenblätter et al. 2003) as well as from brain perfusion experiments in wild type with ABCB1 deficient mice with ABCB1/ABCG2 inhibitor, GF120918, as well as the ABCB1 inhibitor, PSC833, showed transport of prazosin beside mitoxantrone by ABCB1 (Cisternino

et al. 2004). More notably, several chemotherapy medications, including lapatinib, imatinib, and dasatinib, have also been shown to regulate the blood-brain barrier transporter ABCG2 (Shukla et al. 2009; Zhou et al. 2009; Breedveld et al. 2006) which makes it a severe task in the treatment of brain tumors, especially glioblastoma.

13.3.5.1.2 Regulation of ABCG2

Mainly three areas in the blood brain barrier have been thoroughly analyzed in ABCG2 regulation. First is steroid regulation of ABCG2. The brain capillary endothelial cell culture of rat was subjected to dexamethasone for about 24 h to visualization function and upregulation of ABCG2 at mRNA and protein level (Narang et al. 2008). The effect of dexamethasone on ABCG2 was aided by a mechanism based on GR. Recently, the transport activity of ABCG2 was reduced quickly due to the effect of 17-β-estradiol (E2) on the brain capillaries of rat and mouse (Hartz et al. 2010a, b). The effect of E2 was observed to be fully reversible within no time; it does not involve transcription, translation, or proteasomal degradation, representing a non genetic mechanism of signaling. Second regulation of ABCG2 was observed in inflammation. Exposure of 72-h IL-6, IL-1β and TNF-α pro-inflammatory mediators has reduced mRNA and protein expression of ABCG2, in the endothelial cell line of human brain hCME/D3 (Poller et al. 2010). In primary cultures of porcine brain capillary endothelial cells, Wedel-parlow et al. (Poller et al. 2010) confirmed these findings. In these experiments, exposure to both the IL-6 and TNF-α decreased the ABCG2 mRNA for 6 h, while IL-1β decreased ABCG2 protein. By comparison, ABCG2 protein was induced by ET-1. Last is the regulation of ABCG2 in brain cancer. Bleau et al. (2009) showed that in glioma progenitor cells, signaling via PTEN/PI3K/AKT controls the ABCG2 activity. These results were significant because they can potentially be used against brain tumors or brain tumor cells to target ABCG2 to improve brain cancer care.

13.4 Function of ABC Transporters in Alzheimer's Disease

Alzheimer's disease (AD) affects more than 25 million people worldwide, and this figure is estimated to increase to fourfold over 100 million patients by 2050. This rise would increase the cost of global health sector to unimaginable proportions. AD is a debilitating illness, aside from the cost factor. Mentally and physically, AD patients decline and turn performance of human beings to helpless dependents, thus vanishing out existence. There are limited FDA-approved drugs available in the market. Only patients with mild to intermediate AD showed response to these medications but they cause serious side effects. In addition to this, a large number of patients respond to therapy inadequately or not at all. Consequently, new treatments that are directed to the underlying problem causing AD symptoms reverse are today's need.

However, AD is still a mystery, amid decades of scientific efforts; millions of patients with safe and successful treatments remain unavailable. The hallmark

signatures of AD are two proteins, amyloid-β (Aβ) and tau. Aβ's physiological role is still uncertain, but Aβ brain levels are poor in healthy people, while Aβ proportion can be accelerated as many as 100 times in the brain of AD patients, where it becomes cluster of plaques. The proteins associated with microtubules and that interact with tubulin are the tau proteins; they mediate their incorporation into microtubules, thus modulating axonal microtubule stability and flexibility. However, tau phosphorylation leads to cause a disturbance in the organization and structure of the microtubule, and AD hyperphosphorylation of tau protein leads to microtubular collapse and ultimately results in neurofibrillary tangles within the neurons. The hallmark of AD pathology is both Aβ plaques and neurofibrillary tau tangles and is suspected to cause dementia and neurodegeneration. With an emphasis on ATP-binding cassette (ABC) transporters near the blood-brain barrier and in CNS cells, a new AD research area has developed over the last 10 years. ABC carriers use ATP to transfer their substrates through organelles, cells, and tissue membranes. Peptides, lipids, sterols, xenobiotics, and cholesterol, as well as certain toxins and vast group of therapeutic drugs, are the substrates of ABC transporters involved with AD. ABC transporters are considered as an integral element of many physiological as well as biochemical pathways, thus playing a significant role in preserving the homeostasis of the body by extruding metabolites and reducing xenobiotic absorption. Recently, researchers have found that ABC transporters have also played a critical role in diseases where ABC transporter processes and pathways are altered. This role is emerging for some ABC transporters, such as ABCA1, ABCA2, P-gp, MRP1, and BCRP, in AD and other CNS disorders associated with high brain levels of Aβ (Fig. 13.2).

13.4.1 ABCB1

ABCB1 is extensively expressed in excretory as well as barrier tissues, also known as P-gp, which provides good protection against harmful nonpolar therapeutic drugs in addition to xenobiotics. It was discovered in 1989 on human BBB vascular endothelial surfaces (Cordon-Cardo et al. 1989). Accordingly, ABCB1 is also expressed in choroid plexus, neuron, pericytes, and astrocytes (Bernstein et al. 2014). The BBB's ABCB1 facilitates AD (Pahnke et al. 2014) occurrence as well as onset (Pahnke et al. 2014). Different findings have revealed that expression of ABCB1 via BBB has influenced the encephalon transport of endo-xenobiotics (Potschka et al. 2002). Aβ was first reported to interact with ABCB1 by the use of ABCB1-overexpressing HEK293 cells in 2001; this provides solid proof that ABCB1 is an Aβ transporter (Lam et al. 2001). In addition, a clinical discovery showed that the activity of ABCB1, which can be tested in vivo using (R)-[11C] positron emission tomography (PET) and verapamil, is lower in Alzheimer's disease patients as compared to age-related healthy controls (Van Assema et al. 2012). Similarly, ABCB1 insufficiency near the BBB has led to Aβ deposition in P-gp-deficient null mouse in vivo. Additionally, the levels of brain Aβ accumulation were increased in P-gp-deficient null mice relative to P-gp wild-type mice, showing a

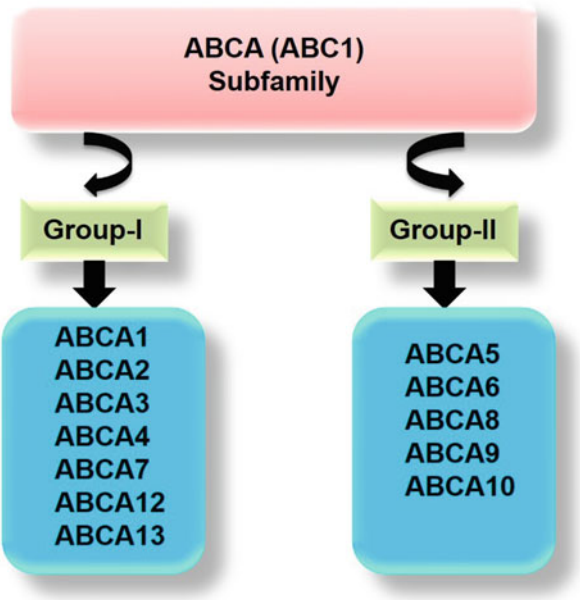

Fig. 13.2 Classification of ABCA subfamily

direct correlation between in vivo Pgp as well as Aβ metabolism (Cirrito et al. 2005). In addition, a substantial decrease in Aβ intensities was observed in APP/PS+/− P-gp wt mice relative to APP/PS+/− P-gp mice which indicates that upregulation P-gp could be a legitimate method to reducing brain Aβ expression (Bruckmann et al. 2017). Deposition of Aβ in the vessel walls was observed in 243 non-demented human brain tissues of blood vessels with very less protein expression of ABCB1 by immunohistochemistry (IHC) techniques in medical temporal lobe, whereas those with higher ABCB1 protein expression displayed lower Aβ deposition, signifying that P-gp might impact the removal of Aβ from the brain (Vogelgesang et al. 2002). Conversely, βABCB1 protein expression as well as ABCB1 action was significantly decreased in endothelial cells of porcine brain treated with Aβ42 for 48 h (Shubbar and Penny 2018). Furthermore, studies have shown that levels of ABCB1 protein decrease during normal ageing at BBB, which is positively associated with Aβ accumulation in AD (Silverberg et al. 2010). Pro-inflammatory cytokines have been found in Aβ-induced AD models, including TNF-alpha, IL-1β, and IFN-γ, and these cytokines will downregulate the levels of mRNA of ABCB1 as well as protein, intruding the unconstructive feedback loop between Aβ and ABCB1 (Alasmari et al. 2018). It has been shown that oxidative stress (OS) in endothelial primary cultured rat cells has accelerated ABCB1 expression as well as activity near the BBB endothelium (Sita et al. 2017). However, there is conflicting information regarding the involvement of ABCB1 to the clearance of Aβ. Likewise, pretreatment of rats with inhibitors of ABCB1 (quinidine and/or verapamil) showed no improvement in the amount of Aβ crossing the BBB in rats (Ito et al. 2006). Collectively, in

the above studies and animal models, the paradoxical findings can be described by using different cell lines, presenting that certain physiological changes can impact Aβ buildup. To treat AD, investigators have discovered a novel therapeutic treatment or medication targeting ABCB1. In vivo studies have revealed that treatment with ibuprofen can reinstate reduced mRNA as well as protein expression of ABCB1 in APP/PS1 mice (Zhang et al. 2018). In another study, it was found that a substrate of P-gp is Huperzine A (HupA) which is an effective inhibitor of acetylcholinesterase (AChE), isolated from *Huperzia serrata*. HupA has been used to target central nicotinic and muscarinic receptors in the treatment of AD and pose neuroprotective properties by inducing strong anti-inflammatory effects (Damar et al. 2016). The brain versus plasma concentration of Huperzine A was considerably improved in Abcb1-deficient mice. Furthermore, the findings indicated that P-gp would mediate the distribution of Huperzine A in brain distribution (Li et al. 2017). Similarly, 1,1-(1,1′-biphenyl]-4–4-diyl) bis(3-(piperidin-1-yl) propan-1-1-one) dihydrochloride (DL0410), a new artificial dual AChE/butylcholinesterase (BuChe) inhibitor for AD cure, presented multidrug properties for AD treatment, for example, refining cognitive deficits, improving synapse loss, inhibiting the activity of cholinesterase, as well as reversing the plaque load produced by Aβ (Zhou et al. 2016; Yang et al. 2015; Lian et al. 2017). P-gp regulated the transport of DL0410 in Caco-2 and MDCK-MDR1 cells, indicating that additional effectiveness along with safety in drug versus drug interactions in AD treatment should be considered (Dodacki et al. 2017).

13.4.2 ABCG2

ABCG2 also called breast cancer (BCRP) protein is found in endothelial cells of BBB and has a defensive role in preventing xenobiotic absorption (Mao 2005). Mounting evidence has shown that in brain endothelial cells, ABCG2 mediates Aβ transport. In vitro studies have shown that the HEK293 cells steadily transfected with human ABCG2 can mediate cellular inflow of Aβ40. In addition, the study also found that GF12918 (a dual inhibitor of ABCB1 and ABCG2) can be blocked by Aβ uptake in ABCB1-deficient mice by means of an in situ brain perfusion procedure, indicating that ABCG2 is also expressed in BBB as well as involved in transport of Aβ40 (Do et al. 2012). In addition, Aβ deposition increased significantly in ABCG2-deficient mice relative after intravenous Aβ injection in wild-type mice, indicating that ABCG2 can inhibit Aβ from entering the brain (Shen et al. 2010). Gene and protein levels of ABCG2 have been increased in the cerebral vessels of patients with AD and mouse models of AD, in comparison to ABCB1 levels (Xiong et al. 2009). The authors proposed that ABCG2 increase could serve as a vascular pathology biomarker for cerebral amyloid angiopathy (CAA). Additionally, after genome-wide analysis it was shown that absence or presence of ABCG2 C/C genotype along with apoE (APOE) is the potent factor for AD pathogenesis (Fehér et al. 2013). The brain endothelium, mediated by ABCG2 (Zhou et al. 2017), can be penetrate certain compounds that prevent Aβ accumulation in AD models.

13.4.3 ABCG4

ABCG4 are half transporter which (Cserepes et al. 2004) often dimerizes with ABCG1 to become stable. ABCG4 is excessively found in endothelial primary cells, glial cells, as well as brain neurons in order to facilitate cholesterol efflux to produce lipoprotein comprising of apoE (Tarr and Edwards 2008; Dodacki et al. 2017). Several studies have found, to the best of our knowledge, that ABCG4 can influence the development and clearance of Aβ. In comparison with ABCG4-KM, a class of walker A lysine mutant of ABCG4, Sano et al. (2016) observed that the elevated APP levels tend to increase in HEK/APPsw cells rapidly transfected with ABCG4. In addition, the author showed that the decreased secretion of Aβ was caused by altered distribution of γ-secretase. They also showed that Aβ secretion was raised during the inhibition of ABCG1 and ABCG4 by SH-SY5Y cells. These researchers argued that ABCG4 could suppress the development of Aβ and the formation of Aβ plaque (Sano et al. 2016). The impact of ABCG4 on the clearance of Aβ from BBB has been documented in studies. In HEK293 cells, stably transfected with mouse ABCG4, mediated the cellular inflow of Aβ. In addition, probucol fully inhibits Aβ efflux from HEK293-ABCG4 cells (Do et al. 2012). Similarly, the authors demonstrated that ABCG4 acts at the luminal surface of endothelial capillary cells in mouse and can transport both Aβ and cholesterol by using an ABCG4-deficient mouse model. The author associated impaired sterol metabolism with competitive inhibition of Aβ efflux as well as progression of AD (Dodacki et al. 2017).

In addition, the study showed that in microglial cells, levels of ABCG4 are considerably increased and could lead to Aβ degradation by phagocytosis (Uehara et al. 2008). There is a need for further studies to investigate the role of ABCG4 in AD pathology which may increase clearance speed of Aβ for AD pathogenesis.

13.4.4 ABCA1

ABCA1, known as the regulatory protein of cholesterol efflux (CERP), is commonly distributed in brain tissues and can induce cholesterol and phospholipid efflux to ApoE. A significant risk factor in AD pathogenesis is cholesterol metabolism impairment in the brain since cholesterol levels are known to increase Aβ development by disturbing BACE1 (Fernández-Pérez et al. 2018). As ABCA1 levels are expressed in the endothelial cells along with neurons of the brain, they do not specifically transport Aβ (Akanuma et al. 2008). ABCA1 can affect the development and degradation of Aβ rather than the efflux in the BBB. The study presented that high level of ABCA1 gene as well as protein induced by LXR ligands might upregulate the concentration of secreted Aβ and might be reversed using the RNAi method by blocking ABCA1 expression (Fukumoto et al. 2002). In addition, homeostasis of cholesterol in BBB models is controlled in vitro by ABCA1 and ABCG1. Bexarotene (an RXR agonist) stimulates the expression of ABCA1, facilitates the exchange of cholesterol amid the blood as well as the brain, and

reduces the inflow of Aβ through the BBB (Kuntz et al. 2015). Furthermore, current study has observed that increase of glucose decreases the expression of ABCA1 and in addition increases the amount of intracellular cholesterol, which controls the localization of LXR alpha/ABCA1 in the lipid raft as well as trigger BACE1 in SK-N-MC cells (Lee et al. 2016). These findings indicate that ABCA1 facilitates lipid and cholesterol rafts in BACE1 APP processing. ABCA1 controls the levels of ApoE as well as lipidation of ApoE, whereas ApoE is known to be a chaperone for Aβ, influencing both its clearance and its aggregation (Holtzman et al. 2012). The Aβ level was discovered to be significantly greater in 12-month PDAPP Abca1−/− mice than in PDAPP Abca1−/− mice without interfering the processing of APP and carbonate-insoluble ApoE co-localized along with Aβ plaques, suggesting that defectively lapidated ApoE co-deposits with insoluble Aβ (Wahrle et al. 2005). The author also found overexpression of ABCA1 in the mouse brain escalates lipidation of ApoE and reduces deposition of Aβ (Wahrle et al. 2008). Similarly, microRNA-33 over expression-induced ABCA1 reduction raises cellular cholesterol as well asthioflavin a type of S- positive plaques, leading to amyloidogenesis (Wijesekara et al. 2016). In the hippocampal area of patients with AD, however, mRNA expression of ABCA1optimistically related with the severity of dementia (Akram et al. 2010). Hence, it can be used as a therapeutic target to aid and assist apoE/Aβ interactions inside the brain by influencing ABCA1 expression and its activity. The current research discovered CS-6253, which could activate directly ABCA1 (ABCA1 agonist), in vitro increase apoE lipidation, and reverse the accumulation of apoE4-driven Aβ and tau hyperphosphorylation. The cause of late-onset AD may be certain environmental and genetic variables. In H4-AβPPs cells, dichlorodiphenyltrichloroethane (DDT) affects the role of ABCA1 which then increases the amount of Aβ (Li et al. 2015). In the general population, ABCA1 N1800H, a functional mutation observed in 0.2% of individuals, was linked with an increased possibility of AD (Nordestgaard et al. 2015). In addition, in three genetic models, ABCA1 rs2422493 (C-477-T) polymorphism is statistically significantly related with an increased threat of AD (Chen et al. 2016). The ABCA1rs2230806 polymorphism reacted well to the treatment of donepezil (DNP) in Han Chinese patients with AD, a drug used to enhance cognition of patients with AD (Lu et al. 2018). Similarly, in AD patients in northern China, the ABCA1 R219 K allele caused a decrease in ABCA1 (Ya and Lu 2017). The small molecular inducer P2X7 was observed to increase ABCA1 as well as ApoE lacking direct activation of the LXR pathway on the basis of the above findings (Fan et al. 2018).

13.4.5 ABCA7

Another CERP, ABCA7, shares a 54 percent sequence similarity with ABCA1 also expressed in endothelial cells of the microglia, neurons, and brain (Kim et al. 2006; Gosselet et al. 2009). ABCA7 facilitates transition of phospholipids as well as cholesterol to lipid-poor apolipoprotein acceptor through cell membranes (Chan et al. 2008). Several groups have shown that ABCA7 can control homeostasis of

Aβ and pathology of Aβ. Research has revealed that ABCA7 acts in the processing of APP, resulting in increased secretion of Aβ that can possibly be related to the action of endocytosis in microglia (Satoh et al. 2015). ABCA7 could also substantially inhibit Aβ secretion in stably expressing APP Chinese hamster ovary (CHO) cells without influencing the activities of alpha- and β-secretases (Chan et al. 2008). ABCA7 deficiency in APP/PS1 mice raises Aβ levels and, in addition, intensifies the burden of amyloid plaque (Sakae et al. 2016). In transgenic mice, ABCA7 deficiency can exacerbate the burden of amyloid in the brain, consistent with these findings (Kim et al. 2013). In microglia, ABCA7 is also active in Aβ clearance. The phagocytic Aβ clearance in microglia in Abca7−/− mice was observed to be significantly decreased in comparison to that in wild-type mice (Fu et al. 2016). In addition, the absence of ABCA7 endothelial cells of mouse induces a decrease in basolateral-to-apical transport of Aβ peptides (Lamartinière et al. 2018). The author has shown that, not directly but in the presence of ApoI-J, ABCA7 affects Aβ transport. Records from multiple genome-wide association studies (GWAS) have revealed that ABCA7 is a risk factor for late-onset AD, the only ABC transporter reported by GWAS (May et al. 2018; Efthymiou and Goate 2017). GWAS has identified several gene variants, for example, ApoE, apolipoprotein J (ApoJ, clusterin), and phosphatidylinositol-binding clathrin assembly protein (PICALM) (Lambert et al. 2009; Harold et al. 2009), which are thought to be known as risk factors for AD. Aβ clearance can be affected by both ApoE and ApoJ. Bell et al. showed that Aβ clearance in the BBB increased when ApoE was bound by LRP1-mediated transport to Aβ, while ApoJ was bound by LRP2-mediated transport to Aβ (Zlokovic et al. 1996; Bell et al. 2007). The ABCA7 SNP rs3764650 sequence was involved in the incidence of AD and is related with a moderate decrease in the expression of ABCA7 (Zhao et al. 2016; Vasquez et al. 2017). In addition, the ABCA7 SNP (rs3764650) is also correlated with the risk of AD in the Chinese population, although its risk may be increased by age and ApoE4 status (Liu et al. 2014). In African Americans, ABCA7 rs3764647 and ABCA7 rs115550680 were associated with risk of AD (Reitz et al. 2013; Logue et al. 2011). In the Spanish population, ABCA7 rs4147929 is correlated with LOAD (Moreno-Grau et al. 2018).

13.4.6 ABCC1

In pericytes, astrocytes, and capillary endothelial cells (Wolf et al. 2012), ABCC1, a strong efflux pump at the BBB, is located on both sides of the brain (Gazzin et al. 2008). The role of ABCC1 in AD has been shown by several studies (Ballerini et al. 2002). In vivo experiments have shown that transgenic mice lacking ABCC1, Aβ40, and Aβ42 levels were elevated in APP/PS1 compared to ABCC1-positive controls (Krohn et al. 2011). Furthermore, scientists discovered that thiethylperazine, an ABCC1 activator, might decrease Aβ load in transgenic APP/PS1 mice (Krohn et al. 2011). These findings indicate that extracts of St. John's wort may be a medicinal medication for AD treatment, which needs more study.

13.5 Potential Alzheimer's Therapeutic Goals

13.5.1 ABCA1 and ABCA2

While ABCA1 and ABCA2 belong to the same subfamily of ABC transporters, their physiological roles and possible involvement in AD pathophysiology are distinct. For proper lipidation of proteins, ABCA1 is essential in the CNS. Reduced levels of ABCA1 protein produce lipid-poor ApoE that tends to escalate the aggregation of Aβ. In AD mouse models, several studies have shown that LXR-mediated upregulation of ABCA1 increases ApoE levels, decreases Aβ brain levels, and has beneficial effects on cognition (Koldamova et al. 2005; Burns et al. 2006; Lefterov et al. 2007; Riddell et al. 2007; Jiang et al. 2008; Donkin et al. 2010). Since there are various compounds available to activate LXR, this strategy may be a possible AD therapeutic strategy. In addition to ABCA1 upregulation, however, activating LXR also raises the level of expression of ABCG1, another ABC superfamily lipid transporter, and ApoE. This is significant as both ABCG1 and ApoE have also been involved in AD (Wollmer et al. 2007). As a result, the useful effects of LXR may be due to the upregulation of fewer types of proteins and may involve other proteins that regulate transport as well as lipid metabolism, for example, Cyp7a1 or the transfer protein of cholesterol ester (Honzumi et al. 2010). Therefore, it is difficult to interpret the findings of the study due the complexity of the LXR regulatory network, and further research is needed to conduct to distinguish the functions of ABCBA1, ABCG1, and ApoE, along with further proteins in AD. Comparative to ABCA1, ABCA2 over expression increases the synthesis of APP, and boosts brain levels of Aβ (Chen et al. 2004; Davis 2010). It means that decrease of ABCA2 can likely decrease brain levels of Aβ and have a beneficial impact on cognition. Till today, there is no research which clarifies the role of ABCA2 as a therapeutic strategy in AD under physiological as well as pathophysiological circumstances.

13.5.2 P-Glycoprotein

P-gp can theoretically be utilized as an AD therapeutic target, given its crucial position in the neurovascular Aβ clearance mechanism. As described above, a novel strategy has been proposed to stimulate PXR, the nuclear receptor to reestablish the blood-brain barrier P-gp, and therefore to minimize Aβ brain load as well as slow cognitive loss (Hartz et al. 2010a, b). Loeb et al. (2004) found that in this respect, patients treated with antibiotics doxycycline and rifampicin having slight-to-moderate AD every day for 3 months in a randomized, triple-blind, and controlled clinical trial substantially slowed cognitive deterioration compared with control group patients. Interestingly, PXR is activated by both doxycycline and rifampicin (Yasuda et al. 2008). Thus, one potential reason for these patients' gradual cognitive deterioration is that rifampicin and doxycycline turn on PXR, which amplified the levels of the blood-brain barrier P-gp, which in turn may have improved the

clearance of Aβ in the brain, dropped the levels of Aβ in the brain, and thus decreased the progressive decline in cognition. However, this theory remains to be confirmed. An alternative technique is to undo the underlying mechanism which decreases the levels of expression and functional activity of the blood-brain barrier P-gp in AD. Awareness of this process could help establish goals for protecting P-gp, maintaining brain clearance of Aβ, preventing slow accumulation of Aβ in the brain, and preventing or delaying AD. In a recent review, the impact of Aβ on blood-brain barrier P-gp as well as expression of LRP in mice was investigated by Brenn et al. Aβ40 and Aβ42 were re-administered for 24 h via an ALZET Mini-Osmotic pump implanted subcutaneously. Researchers found that only Aβ42 significantly reduced the levels of mRNA expression of ABCB1 along with LRP1 in vivo, but no variations were seen at the protein level (Brenn et al. 2011). But rather than prescribing Aβ to the brain, this may have been attributed to peripheral Aβ administration, which would have imitated AD pathology more closely. Further research are not available that discuss the mechanism which reduce P-gp near the blood-brain barrier in AD. Studies undoubtedly show that restoring expression of P-gp as well as function may be effective in improving brain clearance of Aβ and decreasing brain levels of Aβ (Cirrito et al. 2005; Hartz et al. 2010a, b). Though, it is now important to critically evaluate the hypothesis that restore that P-gp at the blood-brain barrier may function as a legitimate therapeutic approach to minimize Aβ brain burden, decreasing cognitive impairment, and delay in advancement of AD.

13.5.3 MRP1

Krohn et al.'s (2011) research is currently the first single proof which indicates a potentially significant function for MRP1 in the in vivo removal of Aβ from mouse brain. More specifically, scientists offer proof of concept of a possible novel therapeutic method for the treatment of AD. There are three crucial points to be discussed. First, it is important to explain the comprehensive miniature mechanism through which thiethylperazine influence MRP1 and probably other mouse (and ultimately human) transporters. Such understanding is important because thiethylperazine tends to activate MRP1 while simultaneously inhibiting P-gp. Furthermore, although the dose of thiethylperazine reduced Aβ brain load, the direct impact on in vivo barrier in blood to brain MRP1 expression and/or functional activity resides indistinct. Second, there is debate about MRP1 place near the blood-brain barrier in humans as well as in rodents. Although few researches indicate that MRP1 is located in the luminal part of the cell membrane, other studies have established expression of MRP1 in the cell membrane (Nies et al. 2004; Zhang et al. 2004; Soontornmalai et al. 2006; Kilic et al. 2008). A current research, though, by Roberts et al. (2008) shows that rat MRP1 is expressed in the brain capillary endothelium on both the luminal and abluminal membranes. Based on this result, the transport of Aβ mediated by MRP1 might occur in one or two directions: (1) by luminal MRP1 into the brain and (2) by luminal MRP1 out of brain into the capillary lumen. Last, there is direct proof that Aβ is transported near the blood-brain barrier

via P-gp; however, for MRP1, such straight proof is unavailable till now. Together, further research is needed to validate existing records to demonstrate clearly MRP1 is highly intricate in Aβ brain clearance as well as a legitimate AD treatment target.

13.5.4 BCRP

Quickly after the first researches were reported on P-gp as well AD, investigators proposed that Aβ is also transported by BRCP and contributes to clearance of Aβ in the brain. The existing information, however, is contradictory, and the role of BRCP in AD is inconsistent as well as inadequate at this point. Although some study shows that Aβ is transported by BCRP (Tai et al. 2009; Xiong et al. 2009), further research indicate that BCRP is not transported via Aβ (Hartz et al. 2010a, b; Krohn et al. 2011). There is also contradictory evidence from AD patient brain samples: BCRP protein levels have been documented to be unchanged at the blood-brain barrier (Wijesuriya et al. 2010); however, other research shows an increase in BCRP expression (Xiong et al. 2009). The conclusion is incompatible to what one can imagine if BRCP led to blood brain clearance of Aβ. One reason for BRCP in AD is that it can serve as a gatekeeper to prevent Aβ from inward the brain at the blood-brain barrier (Xiong et al. 2009). This however varies with the present knowledge of AD etiology, which puts forward that Aβ accumulation in the brain is not due to increased Aβ uptake but rather to decreased brain Aβ clearance. Several problems may lead to these contradictory results. Changes in the expression and/or behavior of transport could, for instance, rest as per AD model, patient or image, and/or inter-individual dissimilarities between patients and research animals.

13.6 Conclusion

ABC transporters are essential factors for the smooth function of the blood-brain barrier. ABC transporters provide protection via efflux and influx mechanism. The transporters efflux the toxic endogenous material out of the cell and thus also provide protection to the CNS and neurons. Going through all the ABC transporters, the involvement of transporters with Alzheimer's disease (AD) is clear. However, researchers are still working for the exact role of ABC to elicit the neurological complications including AD. However, researchers must investigate the immediate effect and signaling in order to discover a therapeutic approach for healthy ABC transporter functions. The effect of genetic heterogeneity, which is a risk factor for the production of AD, needs to be investigated in relation to the loss of neuroprotective function and amyloid beta clearance efficiency of the whole BBB. Aβ oligomers are important in the pathogenesis of Alzheimer's disease. Although it has been shown that impaired clearance increases the amount of Aβ in the brain and increases the likelihood of Aβ oligomer forming, further study on the function of the ABC transporter in clearing Aβ oligomers is needed. Understanding the mechanisms by which ABC transporters regulate and control the development and clearance of

Aβ can show not only the disease-regulating role of transporters but also the pathogenesis of transport disorders in the neurodegenerative phase seen in Alzheimer's disease. The findings in this chapter clearly suggest that the ABC transporter prevents Aβ deposition by regulating the processing or removal of Aβ, thereby protecting the brain, and thus is likely to counteract the progression of Alzheimer's disease. As a result, in the process of developing drugs against these two transporters, further clarification of these transporters, especially ABCB1 and ABCA1, is critical. The two transporters are the most researched, with clear data tying them to the pathology of Alzheimer's disease. Despite some contradictory outcomes from the above text, the findings favor their upregulation as a therapy to improve, heal, or deter disease development.

Henceforth, when regulating ABC transporters, long-term consequences should be considered, such as decreased brain clearance and drug tolerance under transporter induction/activation conditions. Understanding the specific signaling mechanisms that control these transporters could lead to better drug distribution to the brain, which could have a significant effect on the prevention and treatment of brain diseases.

The role of ABC transporters in preserving brain physiology and homeostasis (including regulating Aβ levels) is highlighted in the chapter by their involvement and subcellular and cellular distribution in the brain parenchyma and BBB.

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Autism Spectrum Disorder Relationship Between Sleep and Behavior: The Effect of Sleep Variability Exploration

14

Rokeya Akter and Md. Habibur Rahman

Abstract

While it has been shown that severe sleep issues are normal in children through autism spectrum disorder (ASD), and inadequate sleep exacerbates problem-focused daytime behavior, study and clinical practice have not been very concerned with such relationships. The recommendations on therapy for treating challenging behaviors in ASD do not include sleep or are very minimal. In addition, less attention is being paid to children with low autism, who are frequently affected by extreme sleep disruptions and difficulties with their behavior. This chapter discusses the nature of ASD sleep disorders and emphasizes the implications of sleep disruptions for people with low autism. This is suggested to help understand symptoms and behavior profiles (or vice versa) and thereby contribute to better-targeted treatments by identifying ASD children based on the essence of their sleep disorders. This chapter ends by addressing current knowledge limitations and suggests fields that are essential for future study. The treatment of ASD sleep is highly likely to improve the conduct of the day and the family in this exposed population. In this chapter, we demonstrate the need to define sleep profiles for children with low-functioning autism, particularly for challenging behavior in this condition.

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Keywords

Low-functioning autism · Treating sleep in ASD · Autism spectrum disorder · Exploration

14.1 Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition marked by impairments in social contact and the occurrence of restrictive and repetitive behaviors and desires (Del Barrio 2016). Often people with ASD have issues with mental health, such as observational/powerful behavior, aggressiveness, self-injury, mood swings, hyperactivity and attention problems, anxiety, and sleep problems (Anagnostou et al. 2015). Such problems coexist with the main signs of diagnosis and have an overall effect on the functioning, quality of life, and care results for people living with ASD. ASD is a condition characterized by problems in social contact and repetitive and stereotyped attitudes (Cooper 2017). While ASD's global burden is unknown today, the company costs for this condition were recently estimated in the United States at $126 billion and in the United Kingdom at $34 billion (World Health Organization 2013). Autism is one of the most enigmatic childhood development disorders, with a dramatic rise from 1 in 88 children in 2008 to 1 in 68 in 2010 (Christensen et al. 2016).This rise and economic burden establishes ASD patients as one of the most important clinical research and development priorities. In ASD, the prevalence of sleep disorders is between 50 and 80%. Sleep issues are one of the key concerns posed by child caregivers with ASD (Humphreys et al. 2014; Reynolds and Malow 2011). Sleep performs many functions in a growing child including energy consumption, brain development, consolidation of memory, and cognition (Stores and Wiggs 1998). At present, children through autism with sleep disturbances with more than 40–80% sleep issues, in comparison to 25–40% normally developing children (TYP) is one of the most burdensome concerns of the children with autism (Marrus and Constantino 2016). Owing to the importance of regular sleep, the outcome of sleep issues is potentially serious for people with ASD. Recent work has found inadequate sleep aggravates the frequency of main ASD symptoms (Tudor et al. 2012; Liu et al. 2006) and other ill-adaptive behaviors (e.g., self-injury, tantrums, and violent behavior) (Henderson et al. 2011; Ferguson et al. 2019). The association between sleep profiles and behavior issues in people through ASD has been limited to date. The basic nature of the disorders in people with low autism cannot be addressed by present sleep therapies. In this chapter, we demonstrate the need to define sleep profiles for children with low-functioning autism, particularly for challenging behavior in this condition.

14.2 Autism Spectrum Disorder Sleeping Problems

ASD also leads to comorbid disorders and related symptoms, including sleep disorders (Matson and Rivet 2008; LoVullo and Matson 2009). Poor sleep among parents and caregivers of ASD is one of the most burdensome and heavy complaints. Evidence suggests that about 40–80% of people with ASD are sleeping, and the risk does not seem to depend on the extent of cognitive impair (Cortesi et al. 2010). Other findings found that individuals with low autism are more vulnerable than those with higher function, despite the degree and extent of their cognitive disorder, to recurrent dormant process disturbances (Sajith and Clarke 2007). This chapter suggests that recognizing, defining, and treating low-functioning autism sleep disturbances may have beneficial effects for related symptoms and daytime behavior and thereby enhance the lives of this group.

14.3 Autism and Poor Functioning

ASD is known for its extraordinary phenotypic heterogeneity, also considered an obstruction to the investigation of diagnosis, etiology, treatment, and prediction (Charman et al. 2011). The degrees of disability of ASD people are variably described as having a rational proportion that is not as large (<70) and higher (T70), correspondingly. The level of disability is therefore variably different among individuals who have low autism and high autism (Battle 2013). In addition to the signs of core ASD, many children with low autism can have extreme behavioral problems including tantrums, violence, environmental damage, a socially deficient behavior, and self-injury (Kanne et al. 2011). The new DSM-V are the far bigger impairments in people with low autism than those encountered by their more successful peers (Ni Chuileann and Quigley 2013). There is also a much more nuanced medical image of children with low-working autism, with more ASD symptoms and related co-morbidities, and a broad intervention for children over a lifetime. To date, equal consideration has not been extended to these groups of people about individuals through high-functioning autism.

14.4 ASD and Other Psychological Symptoms

A third possibility is that sleep disorders are entirely irrelevant to ASD. The association between sleep disturbances and related psychiatric comorbidities in people who have ASD is significant in this context. Sleep disorders can exacerbate related psychiatric symptoms such as interference or abuse (Daroff 1991). In comparison, medical conditions like attention deficit/hyperactivity disorder (ADHD) can also be linked to exacerbating sleep disturbances in individuals with ASD. It is characterized by difficulty with social communication as evidenced by "deficits in social-emotional reciprocity deficits in nonverbal communicative behaviors for social interaction deficits in developing, maintaining and understanding relationships"

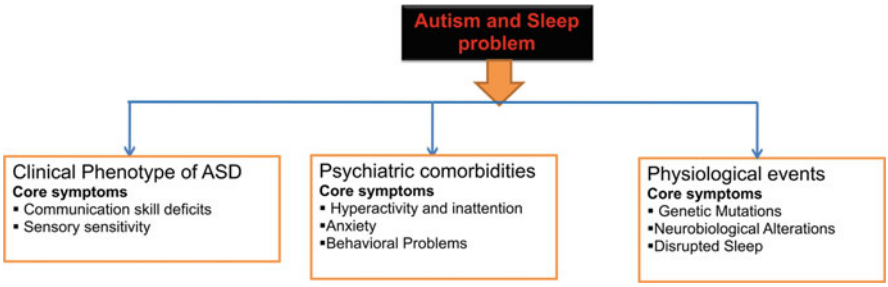

Fig. 14.1 ASD and sleep-associated problems symptoms

(Liu et al. 2017). People with ASD are often represented literally, directly, honestly, steadily, and loyally in plain language (Conte 2021). Many people with ASD are distressed by unanticipated schedule changes or unexpected events and tend to thrive with rules and routine (Henry 2020). ASD and sleep-associated problems are shown in Fig. 14.1.

14.5 Sleep Disorder Variation in ASD

ASD is seen as a multifaceted condition with various symptoms in individuals, it is no wonder that many sleep disorders in this population are prevalent. Furthermore, the sleep pattern variation in ASD indicates mixed phonotypical ASD sample profiles. Excessive sleep delay, decreased sleep duration, declared sleep time, increased sleep wake, and sleep resistance for 1 day are the most common problems for children with ASD; see (Hollway and Aman 2011) for further review. Therefore, sleep problem that is common for ASD children, but others. Such sleep issues seem to continue throughout the patient's life (Matson et al. 2008a), and individuals with ASD who have an ASD problem also suffer from sleep problems together (Rong et al. 2021; Souders et al. 2009). Several of those issues can be categorized as a primary sleep disorder (e.g., insomnia, parasomnia, and circadian sleep-wake diseases) under the International Classification of Sleep Disorders (ICSD-3) (Daroff 1991). Table 14.1 displays mainly the common sleep problems in ASD, according to ICSD-3, to provide a sense of the sleep spectrum and severity of difficulties in ASD. To date, several sleep research studies at ASD have concentrated on individuals who can communicate with and participate in sleep actigraphy and polysomnography with high-functioning autism (Allik et al. 2008). The existence and occurrence of sleep disorders in low-functioning autism is generally unclear. The cruelty of sleep disorders (such as sleep and sleep delay) and the extent of autism symptoms (e.g., communication deficits) was shown by one study (Tudor et al. 2012). One research has indicated that the increased severity of the autism causes an increased risk of sleep difficulties, but these linkages are still uncertain, and low-functioning autism sleep profiles have not yet been explained. To date, precise sleep patterns and symptoms of low autism persons remain unknown.

Table 14.1 ICSD-3 Sleep disturbances in children through ASD with a description and confirmation identification

ICSD-3 classification	Sleep summary	Study	Sleep actions	Significant findings of the ASD population
Insomnia	The initiation of sleep, treatment, length, consolidation, or coherence is an ongoing issue	Wiggs and Stores (2004)	Actigraphy and SQ	Increased latency of sleep, night awakens, and low sleep effectiveness
	Includes resistance to sleep, regular night awakenings, and/or sleep failure	Malow et al. (2014), Deye et al. (2016)	PSG and CSHQ	Sleep quality decreases, sleep takes longer, and wakes occasionally at night (2–3 h)
		Goodlin-Jones et al. (2008)	Actigraphy and SD	Sleeping time is lower in comparison with TYP or DD children
		Krakowiak et al. (2008)	SQ	Improved sleep and night awakenings in contrast to traditional children
		Anders et al. (2011)	Actigraphy and SD	ASD children 2 years of age slept on average less than controls for 24 h every 24 h
Parasomnias	Undesirable physical sensations that take place during sleep or sleep excitement. Features nightmares, wake screams, dynamic movements,	Hering et al. (1999)	Actigraphy and SQ	54% of children have numerous and early night anticipation with ASD
	Hallucinations and unconscious movement of the nervous system	Doo and Wing (2006)	SQ, CSHQ, and actigraphy	All studies indicate higher parasomnia rates in children with ASD in accordance with similar groups
		Schreck and Mulick (2000)		
Circadian rhythm sleep-wake disorders	Changes to the circadian time keeping system, its function for preparation, or misalignment of the external and endogenous circadian rhythm manifestations in sleep initiation and maintenance difficulty	Giannotti et al. (2008)	PSG and CSHQ	10% of children living with ASD reported problems with sleep that differ by season as light/dark cycle fluctuations
		Tordjman et al. (2013)	Measures of melatonin	Strong routine and weak nocturnal melatonin relative to controls in individuals with ASD

14.6 Behavioral Problems

Children with ASD also have several issues, including agitation, violence, self-injury, hyperactivity, impulsiveness, and noncompliance (Postorino et al. 2017). Such behavioral issues raise parental stress and negatively impact family life quality (Dabrowska and Pisula 2010; Mugno et al. 2007). Several studies have shown that sleep disorders can intensify behavioral issues in people with ASD (Patzold et al. 1998; Goldman et al. 2011). For example, in a study of 45 children with ASD, Fadini et al. (2015) established that sleep disruption was connected with the use of the Child Behavior Checklist (CBCL) for thinking and complete behavioral issues. In 166 kids with ASD relative to 111 uninfluenced babies, Park et al. (2012) reviewed the sleep disorders and their correlations with comorbid psychoanalysis. The authors find that children with ASD and sleep disorders are more likely than children who are not sleep-impaired to engage in violent behavior, internalize, externalize, and have total problems of behavior. This result supports the idea that improving the sleep of young children can reduce behavioral problems for children and in effect can reduce parental stress and improve the functioning of the family. One of the study on the practice route in children and youths with ASD for detection, assessment, and management of insomnia indicates to pharmacological treatment (i.e., melatonin) might be suggested in certain circumstances (Malow et al. 2012). Parents with kids with ASD and sleep disorders should also use tools to cope with these disorders. The function of parents in lessons them techniques to avoid or react to such behaviors is commendable for parent training as the first-line intervention model. Competent measures such as sleep hygiene in children with ASD are successful in managing sleep difficulties (Dunn et al. 2012; Loring et al. 2016; Pattison et al. 2020). Randomized controlled trials by Johnson and others have shown the feasibility and initial efficacy of parent training interventions in sleep disorders in a population of well-characterized young children with ASD (Johnson et al. 2013). Several features in ASD were identified for early disorder characterization and are often referred to as "Red ASD flags" (Leaf et al. 2020). Symptoms of ASD and features usually occur at the age of 2, and most ASD children prefer solitaire, no pretense, or symbolic play up to this age as well (Leader et al. 2020).

14.7 Over-Activity and Carelessness

Hyperactivity and inattention to ASD are frequently found in children with ASD, with about 30% meeting the diagnostic requirements for ADHD (complicated hyperactivity disorder with attention deficit) (Simonoff et al. 2008). Numerous research found that children with ADHD are experiencing serious sleep disturbances including erratic sleep, sleep disruptions, insomnia, and finally day sleep (Singh and Zimmerman 2015). The presence of these signs may also increase the probability that people with ASD may suffer from sleeping disorders. DeVincent et al. (2007) also showed that ASD children with sleep issues have had higher ADHD levels compared with children without sleep problems as they investigated the associations

between sleep problems and psychological symptoms. Wheelwright et al. 2010 also concluded that ASD weaker sleepers had greater recorded inattention, hyperactivity, and restricted/repetitive behavior in the assessment of the probable effect of parental sleep issues on sleep planning during objective trials (e.g., actigram). Also care for symptoms of ADHD, such as methylphenidate, drugs are recognized to interfere with sleep and even to boost sleep issues. Sangal et al., for example, noticed in a randomized, two-blind crossover study (Sangal et al. 2006) that sleep-induced latency was substantially higher than that of atomoxetine in 85 ADHD infants with methylphenidate.

14.8 Treating ASD Children's Sleep Disorders

Significant sleep disorders in children with autism are increasingly apparent, but little study has been carried out in this population on the evidence of sleep treatments (Knight and Johnson 2014). Sleep disturbances in ASD are often untreated and ignored because many behavioral issues continue to prevail (Cortesi et al. 2012). By contrast, research has shown that melatonin is helpful even to kids with ASD who suffer from sleep latency problems because night wake is known to increase and to disrupt sleep maintenance (Rossignol and Frye 2011). Some research promotes the effectiveness of melatonin in reducing the duration and increasing the total amount of sleep when administered near bedtime (Goldman et al. 2014; Dodge and Wilson 2001). Effective intervention for improving the start of sleep and maintenance in ASS has been shown in the conduct of interventions such as sleep hygiene strategies aimed at environment change to facilitate daily sleep-wake cycles (Weiskop et al. 2007). The potency of melatonin is also affected by sleep disturbances and environmental and other medical conditions (Damiani et al. 2014). Despite the absence of biological causes, the first diagnosis of sleep disturbance in ASD is parent-based education and behavioral strategies (Grigg-Damberger and Ralls 2013). The concepts regulating sleep hygiene include the selection and setup of a suitable bed, increasing TV views, and stimuli for emotion and action during the night. For patients with circadian sleep disturbances, light treatment is efficient for progressing or delaying the sleep period, and it may be recommended for children with circadian disruption of an ASD (Miano et al. 2007). However, light therapy is limited in studies for people for poorly functioning autism. This advanced clinical therapy is suitable for people with low autism who have little to no spoken abilities on average. The efficacy of conduct treatment strategies currently is therefore dependent on small trials and lacks quantitative sleep metrics. Children with a range of conditions not limited to ASD have now also been included (Malow et al. 2014). Due to the correlations between insufficient sleep, increased daytime issues, and parental pressure in ASD, successful sleep strategies tailored to the cognitive and developmental level of children are very important.

14.9 The Correlation Between Bad Sleep and Problematic ASD Behavior

Sleep disturbance is associated with emotional and compartmental issues including internalization and externalization of symptoms during typical development (Malow et al. 2014). However, increasing evidence indicates that child sleep issues can make a big difference to the well-being, actions, attention, cognition, and school performance of children (Chen et al. 2006). Lower sleep hours were associated with greater ASD severity and were predictive, including deficiencies in social skills (Richdale and Schreck 2009), cognitive defects, higher expectations, and tighter observance of nonfunctional routines (Schreck et al. 2004). Due to its nature, the consequences of sleep disturbance in this condition are potentially significant, given the associated destructive behavior. ASD signs have been compounded by sleep disorders. As well as aggravating the symptoms of ASD, sleep disorders have also been demonstrated to be associated with increased over-activity levels, agitation, noncompliance, aggressiveness, irritability, and affective issues that can all greatly interfere with the daily functioning. Despite studies into the association between sleeping disturbances and challenging ASD performance, the effect of sleep issues was overlooked for children with low autism (Schreck et al. 2004). Therefore, the two-way interplay between sleep and actions was small. Sleep disturbance is usually linked to emotional and conduct issues including the internalization and externalization of symptoms (Wang et al. 2020). ASD signs have been exacerbated by sleeping problems. Less time sleep was associated, and more serious ASDs such as social ability deficits were predicted. Knowing the severity of sleep disorders in ASD, it is apparent that sleep can be modified in certain populations with ASD (Richardson and Friedman 2016). In addition, sleep treatment has been shown to increase the core symptoms of ASD in a group of people with ASD (e.g., communication and socialization impairments) as well as to decrease the severe behaviors of ASD (Kruppa et al. 2021). The association between sleep difficulties and inappropriate behavior for children with ASD indicates further study is necessary to determine the direct links between specific sleep issues and the specific daily patterns of behavior that might affect people with ASD (Kruppa et al. 2021).

14.9.1 Mood Disturbances and Anxiety

Anxiety was also observed in children and adolescents with ASD, and a meta-analysis found that 39.6% of young people suffering from ASD had clinically high levels of anxiety or at least one anxiety disorder (van Steensel et al. 2011). Research has shown that anxiety is related to psychological hyper-arousal, which in turn can exacerbate sleep and sleep problems (Krämer et al. 2012; Monk et al. 2001). In reality, anxiety can trigger distracting thoughts and concerns during pre-sleep periods, interfering in the onset of sleep. Different studies have shown that anxiety and mood disorders can worsen sleep disorders for typically developing children (Owens 2007; Cortesi et al. 2010; Van der Heijden et al. 2018; Medic et al. 2017).

Similar research also found that anxiety is correlated with insomnia, though insomnia can lead to depression (Johnson et al. 2006; Jansson and Linton 2006). Mood disorders, for example, depressive or bipolar disorders, have also been documented frequently in people with ASD (Simonoff et al. 2012). Both conditions were also associated with abnormal or hyper-arousal cognitive function. It is known, for example, that people with bipolar disorders may suffer from decreased sleep requirements (Gold and Sylvia 2016). An increasing amount of studies recommend that anxiety and mood symptoms are also related to sleep disorders for people with ASD (Paavonen et al. 2008; Quine 1991). A survey of 477 autism children also showed a significant rise in family issues with maternal anxieties and mood symptoms (Mayes and Calhoun 2009). For example, Nadeau et al. (2015) found that a number of issues with sleep were associated with the internalization and externalization of symptoms and the symptoms of anxiety in a study of 102 children with ASD. Past research of anxious children has shown that management of these symptoms improves sleeping conditions (Alfano et al. 2009). These symptoms may minimize problems in sleep even in people with ASD. It is possible. Nonetheless, more research into the potential of reducing sleep disorders is also needed in the psychological or pharmacological treatment approaches tailored to the wants of young people with ADS.

14.9.2 Future Guidance: Sleep and Activity Relationship in ASD

The latest research indicates that people with ASD have a strong one-way relationship between sleep and behavior. Sleep disorders are well-known to aggravate and exacerbate symptoms of ASD in most important areas. These interactions have been studied very well with people with mixed groups of ASD populations and with people with high-functioning autism in a cross-sectional research. Target tools like polysomnography and wrist actigraphy (a tool which measures physiological conditions during sleep, like an electroencephalogram) were used to confirm the associations between bad sleep and daytime behaviors in a mixed sample of ASD kids (Knight and Johnson 2014; Goodlin-Jones et al. 2009). With the severity awareness of sleep disturbances in ASD, sleep in some populations with ASD is modifiable. (Reed et al. 2009). For children with autism, medication intervention including melatonin is an important sleep intervention (Guénolé et al. 2011). Moderate evidence is also available that holistic parent monitoring interventions as the CSHQ are a high-level single-point response intervention to help determine childhood ASD sleep efficiency (Hodge et al. 2012). Sleep therapy has shown that the principal symptoms of ASD in a subgroup of ASD individuals are improved and complicated activity in ASD is decreased (Tordjman et al. 2013). Taking into account the two-way correlation between sleep disorders and challenging behavior in ASD, preliminary research indicates that sleep disorder and sleep disorder do not result in positive outcomes in isolation (Richdale et al. 2014). ABA (applied behavior analysis) therapy is known to be effective in helping a subset of children with ASD with disruptive behavior; it is known to affect learning levels and

cognitive efficiency. Furthermore, the effects are affected by the consistency of learning. Since sleep is involved in learning behaviors including obedience, irritability, hyperactivity, and aggressiveness, more research is now emerging to show that sleep can be an obstacle to ABA care with ASD (Russell et al. 2013). The association between sleep issues and inappropriate behavior, which has been listed for children with ASD since daytime, indicates that more work is needed to establish direct ties between such problems and everyday comportment habits that can influence individuals with ASD.

14.9.3 Further Fields of Study

As mentioned, recent work primarily focuses on more productive ends of autism and literature in people with low autism who may have the most serious problems in sleep and behavior. However, though recent studies have shown strong connections between inadequate sleep and problematic behaviors in ASD, it is still unclear, as discussed above, how special the particular issues are in sleep and symptoms of people suffering from low-functioning autism. The study of sleep in children with poorly functioning autism poses particular analytical challenges. Biased parental accounts impart bias, negative halo effects (Souders et al. 2017), and individuals with sensor sensitivities or lack of engagement have difficulty tolerating objective intervention, such as PSG and actigraphy (Hodge et al. 2012). To date, very few studies have been performed longitudinally on compartmental problems and ASD sleeping conditions, most of which have been cross sections. Transversal studies often investigate a single age group, and the majority of research includes mixed children and adolescents. Since children with ASD are listed as one of the most significant priority sleep research populations by the National Sleep Foundation (Mindell et al. 2009), more accurate, reliable, nonintrusive sleep measures and child autism data are needed to better define sleep quality and quantity in this population. It is understood that the extent of ASD and behavioral disorder wax and fall over development with some activity that improves with age (Matson et al. 2008b). Since various behavioral patterns are found in particular ages and maturity age does not always correlate with chronological age in ASD, longitudinal designs are important for researching relationships. Up to now, only one study examines retrospective, high-functioning autism and usually improves regulation oversleep disturbance and behavior. Little is understood how sleep changes over time in ASD and how variables such as age and stage of development can be associated with this transition. The research found no association between sleep difficulty and developmental period (i.e., childhood, adolescence, and adulthood) in ASD (Delahaye et al. 2014) although sleep difficulties with age decreased with other tests, albeit cross sectional, comparable to normal developmental difficulties (Giannotti et al. 2008; Goldman et al. 2012). Therefore, further longitudinal studies are necessary to monitor the pathway to sleep in this population to recognize key ASD phenotypes and link these to sleep profiles. For example, sleeping problems in ASD can vary with medication, climate, or comorbidities like epilepsy or GI problems. Whether co-occurring

disorders cause behavioral issues or continue to present problems, or exacerbate existing ASDs, is difficult to determine. To answer this poignant question, research must be carried out. To improve sleep and to promote more optimistic predictions by improving day-to-day actions and family functioning in that population, it is important to recognize and provide treatment for sleep problems in ASD. Studies have a common proposal that factors resulting in the ASD phenotype should be identified and instead tailored therapeutic measures designed to restore or minimize particular deficits. Eventually, treatment recommendations for helping people with low autism to handle difficult behavior often do not include sleep or are rather minimal in scope. ASD sound resistance may be correlated with lower waking thresholds, sleep fragmentation, etc. This chapter suggests that identifying ASD children with sleep disturbances based of the essence of their sleep issues may help them understand signs and behaviors (or vice versa). The exposure of children with low-functioning self-regulation behavior (such as self-harming behavior) can, for example, increase sleep and sleep latency before they go to bed until they sleep and become sleepy. Increased light sensitivity from exposure to the device and/or tablet blue-enriched light may also be correlated with circadian timing and melatonin issues, which contribute to increasing sleep-wake circadian patterns in this population.

14.10 Concluding Remarks

Although severe sleep disorders are common in children with ASD and inadequate sleep exacerbates the everyday behavior of particular problems, the results are premature. A new avenue for the advancement of procedures is provided by having a more detailed insight into the human existence of sleep problems at ASD as sleep is an environment that can be remedied. Because sleep is a key physiological process (e.g., learning, memory, neuroplasticity), sleep disturbances play a key role, including the exacerbation of problematic behavior, in ASDs. Nonetheless, to date, studies have failed to offer conclusive proof of the connection between sleep and actions in people (of all ages) who are poorly functioning with autism. This review underlines the importance for children with ASD to identify sleep profiles and to include various aspects of their symptom profiles in sleep deficiencies (and vice versa). In addition, this knowledge results in new therapeutically strategies and action that, in 68 individuals impacted by this overall developmental condition, will ideally enhance the long-term outcomes.

Conflicts of Interest Authors declare that he has no conflict of interest.

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Cognitive Impairment and Rehabilitation of Children and Adults with Autism Spectrum Disorder

15

Fauzia Nazam and Akbar Husain

Abstract

Since 1943, when Kanner introduced the term "Autism," there has been much progress to identify the nature of impairment in autism spectrum disorder (ASD) among adults and children. Currently, it is classified as a neurodevelopment disorder marked by impaired social cognition, altered sensory stimulation and language deficiency with or without impaired IQ. Despite having clear diagnostic criteria, the heterogeneity in cognitive, language and intellectual abilities across type and ages perplexes the clinical picture of ASD and needs clinical expertise for diagnosis. This chapter outlines the nature of ASD and types of impairment broadly classified in the area of cognition, speech and language, intelligence impairment and executive dysfunctioning. Furthermore, the chapter highlights a range of rehabilitative technique for person with ASD, namely, dialectical behaviour therapy (DBT), cognitive behaviour therapy (CBT), pivotal response treatment (PRT), sensory motor training, parent-mediated intervention (PMT), speech therapy, music therapy and sensory integration therapy. This chapter has also highlighted the current scholarly debate about ASD and DLD (developmental language disorder) categorically different or on the same continuum.

Keywords

Autism spectrum disorder · Social cognition · Cognitive behaviour therapy · Dialectical behaviour therapy · Music therapy · Speech therapy

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In 1943, Kanner used the term autism, which is derived from Greek word "autos" meaning "self" and "ismos" meaning "Action". Autism spectrum disorder (ASD) is a neurodevelopmental disorder (Suthar et al. 2020) characterized by the deficit in social communication and interaction, social and emotional reciprocity, nonverbal communication behaviour (e.g. inability to maintain eye contact, facing away from the listener), developing and maintaining relationship, problems in adjusting to new social context (e.g. absence of interest in others), restricted and repeated behaviour (e.g. a typical speech or movement), excessive routine rituals, fixed interest and hyper-/hypo-reactivity to sensory stimulation (e.g. indifferent to pain, altered vigorous and truncated sniff response, odour identification impairment, hypo-discrimination for sour and bitter taste, i.e. lower taste discrimination, etc.). The symptoms are present in early childhood and cause marked impairment together in everyday functioning (Hyman et al. 2020; American Psychiatric Association 2013). Cognitive, language and intellectual challenges are the major diagnostic criteria for ASD (Hus 2017). Although there are well-defined diagnostic criteria, the heterogeneity in cognitive, language and intellectual abilities across the type and age differentials perplexes the clinical picture of ASD. Children with regression type exhibit more impaired cognitive and social abilities as compared to non-regressive type around the age of 28 months since birth (Matson et al. 2010). Furthermore, compared to early-onset type of ASD among the regression type, symptoms manifest until the age of 2 years proceeded by regression, whereas among children of early-onset type, symptoms manifest soon after birth (Barbeu 2017). A study has found differential IQ in the sample of 156 children with neonatal and regression type with age range of 10–14 years ($M = 11.7$, $SD = 0.9$), where 3% of children were above average IQ (>115), 28% had average IQ (85–115), 16% had below average IQ (<50) and 55% intellectual disability (<70) (Charman et al. 2011). In this chapter, we describe the cognitive impairment and rehabilitation aspects of children and adults with ASD.

15.1 Cognitive Impairment

Mere sensory and perceptual impairment is the classical way of looking at ASD. The DSM-5 (American Psychiatric Association 2013), has shown an improvement and shift of focus to the impaired social cognition (SC), as a key feature of ASD among children and adults. In the new development of literature, the disorder is largely characterized by impaired socio-cognition and language/communication deficiency. Researchers have examined the association between general/specific intelligence and social cognition. Skuse et al. (2009) have found significant correlation between higher verbal IQ and social communication. A recent study has also found low general intelligence hindering social cognition, but up to a certain threshold. They further added that increased intelligence does not add outstanding social cognition in ADS children (Hirosawa et al. 2020).

15.1.1 Social Cognition (SC)

Social cognition includes social motivation, social recognition, social attention and social learning ability (Happe et al. 2017). This is important in the positioning of "self" while interacting with others (Isaksson et al. 2020). Alteration in these abilities is presumed as impaired in SC. Negative alteration in SC is associated with increase in ASD symptoms and autistic trait (Isaksson et al. 2020). While explaining SC among adults with ASD, "theory of mind" (ToM) provides useful findings. ToM relates with the ability to recognize other's mental state to understand and predict people's behaviour. Recent research has recognized ToM as an important social cognition ability, which helps in making meaningful social interaction and maintaining interpersonal relationship (Baksh et al. 2020). ToM has cognitive and affective domains. Adults with ASD have both types of impairment (Murray et al. 2017). Recent advances show that children with ASD manifest preference to non-social stimuli over social stimuli. Gale et al. (2019) conducted an empirical study to test the social motivation of ASD children. They presented abstract moving geometrical figures (non-social stimuli) and films of faces of young adults (social stimuli) to ASD children. It was found that the children preferred geometrical figures over human faces. This finding supports that ASD children lack social motivation in the sense that preference of non-social stimuli over social stimuli signifies greater reinforcement strength of non-social stimuli and tendency to avoid social stimuli. Avoidance of social stimuli may lead to deficit attending faces and eyes of caregivers or listening human voices which may act as an additive factor of low social communication.

15.1.2 Non-social Cognition

There is a great research interest about the nature of impairment among children with ASD, and comparatively less researches have focused on the nature of impairment among adults with ASD. In children, largely social cognition impairment is a focal area of research, and non-social cognition deficit is an understudied aspect of it. It refers to reasoning, problem-solving, attention, vigilance, verbal learning and memory. Recently, non-social cognition was studied among adults with ASD. A meta-analytical review shows statistically largest impairment on information processing speed, followed by verbal learning, memory, reasoning and lastly problem-solving skills among adults with ASD (Velikonja et al. 2019). This finding clearly demonstrates that at different stages of life, ASD probably shows different kinds of impairment. However, the external validity of this finding is subjected to multi-cultural prospective studies.

15.2 Language and Speech Impairment

The second kind of impairment is related to language which is an important aspect of human cognition. Studies have reported that children with ASD have difficulty in producing the complex sentence structure specifically sentences with relative clause (e.g. The chocolate that Sam had yesterday, was made of dark chocolate and milk) (McGregor et al. 2012; Riches et al. 2010) and producing the repeated sound; therefore, they omit the speech sound (Cleland et al. 2010). Notably the reduction in the use of tense while sentence making and speaking is very common (Modyanova et al. 2017; Roberts et al. 2004; Tager-Flusberg 2015). Morphosyntactic deficit is another visible language deficiency in this case (Gladfelter and Barron 2020; Riches et al. 2012). Similar language deficiency is observed in developmental language disorder (DLD); therefore, the current scholarly debate is whether ASD and DLD are the categorically different disorders or they are on the same continuum (Gladfelter and Barron 2020). Adults with ASD also reported communication difficulty (Lewis et al. 2008). Recently, a qualitative study was conducted to examine the autistic adult's view of their communication skills and needs. Through thematic analysis of their experiential orientation, it was found that autistic adults presented a complex communication difficulty (e.g. inability to find the word while public speaking). This difficulty further exacerbate while conversing with strangers as compared to the people with spectrum. They experience intense anxiety while communicating (Cummins et al. 2020).

15.3 Intellectual Impairment

The third kind of impairment is intellectual impairment. The intellectual impairment and autistic symptoms are mostly not mutually independent of each other in ASD. For example, repetitive and restrictive behaviour (RRB) (e.g. typical movement) is found to be correlated with low non-verbal quotient (Bishop et al. 2013; Hirosawa et al. 2020; Riches et al. 2010). There exists negative correlation between RRBs and non-verbal IQ among ASD children (Kim and Lord 2010; Ray-Subramanian and Weismer 2012). In fact, the first description of autistic disorder given by Kanner (1943) included delayed intellectual development. Although Intellectual Disability (ID) is a separate disorder under DSM-5 as a Neurodevelopmental Disorder characterized by the significant impairment in intellectual functioning (IQ <70) and adaptive functioning prior to 18 years of age (Ropers 2010). Epidemiological studies report that 30% of ASD children also have ID. DSM-5 specifies the diagnosis of ASD "With or Without Intellectual Disability" (Thurm et al. 2019). Presence of RRBs in both the disorder makes them more proximal to each other. ASD can persist with or without ID; therefore, diagnosis requires more clinical expertise (Thurm et al. 2019).

15.4 Executive Dysfunction (ED)

Executive dysfunctioning is the fourth type of cognitive impairment among individuals with ASD. 41% to 78% of individuals with ASD experience issues related with executive functioning (EF) (Lynch et al. 2017). It impacts neurocognitive, psychosocial and behavioural aspects of ASD personalities (Leung et al. 2016; Pugliese et al. 2016). Executive functioning involves proper functioning of working memory, cognitive flexibility, inhibitory control and planning abilities (Christ et al. 2017). Working memory helps in active manipulation of sensory information for a relatively shorter period of time compared with long-term memory (LTM). Inhibitory control is the ability to suppress activation and processing of sensory information which could interfere with cognitive goals. Executive dysfunctions are operated by the prefrontal cortex (PFC), a part of the frontal cortex. The frontal lobe helps in memory, reasoning, problem-solving and decision-making. It is found that people with ASD irrespective of ages and functional level have this kind of impairment. Impairment in cognitive flexibility, planning, working memory and self-monitoring is the most prevalent among individuals with ASD (Cassidy et al. 2014; Zinke et al. 2010). A recent study in this context among children recorded highest impairment in organizing ability, followed by working memory, emotion control and self-monitoring. Significant difference was not found on executive dysfunction related to age differential of children. Therefore, it is suggested that executive dysfunctioning among ASD children remains stable across all ages (Alsaedi et al. 2020) (Fig. 15.1).

The following section covers the rehabilitation aspect of children and adults with ASD.

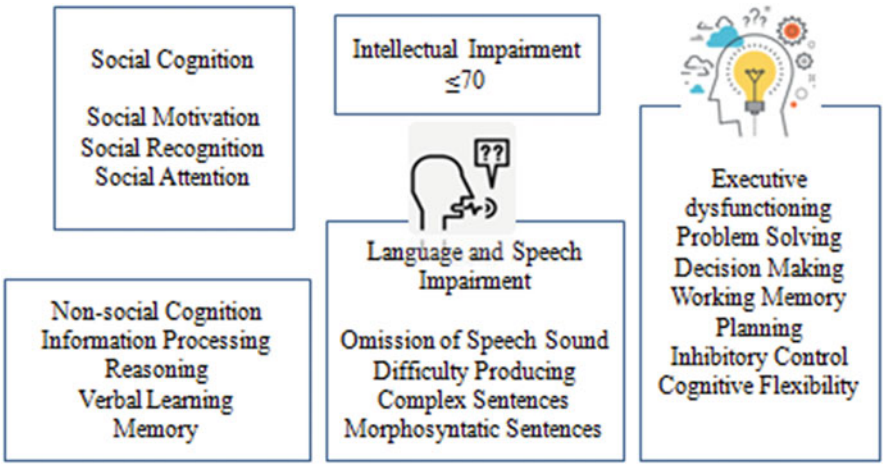

Fig. 15.1 Showing cognitive impairment in autism spectrum disorder

15.5 Rehabilitation

The meta-analytic review of epidemiological study shows less prevalence of ASD in Asia (Bangladesh 2018 0.76/1000, India 2017 2.19/1000, China 2014 2.75/1000, Nepal 2018 3.42/1000) compared to the European countries (Sweden 2011 14.4/1000, Poland 2014 5.29/1000, Germany 2012 6.50/1000) (Chiarotti and Venerosi 2020), but since Asian countries are more populous, therefore we could expect a rise in the prevalence rate. Thus, we consider that it is important to discuss the types of rehabilitation that is needed for children and adults with ASD (Fig. 15.2).

15.5.1 Dialectical Behaviour Therapy (DBT)

In the 1990s, dialectical behaviour therapy (DBT) emerged as a rehabilitative technique for suicidal behaviour and borderline personality disorder. But researches have found similar suicidal ideation in ASD patients (Hedley and Uljarević 2018; Segers and Rawana 2014). Hedley and Uljarević (2018) have found that 25% of the total ($N = 76$) adults with ASD had clinical range of depression and 20% had suicidal ideation. They also found that perceived tangible support was a protective factor against suicidal ideation. ASD patients manifest depressive thoughts also (Dickerson Mayes et al. 2014; Cassidy et al. 2014). In ASD, the deficit in emotion regulation and lack of control over affective state are associated with suicidal

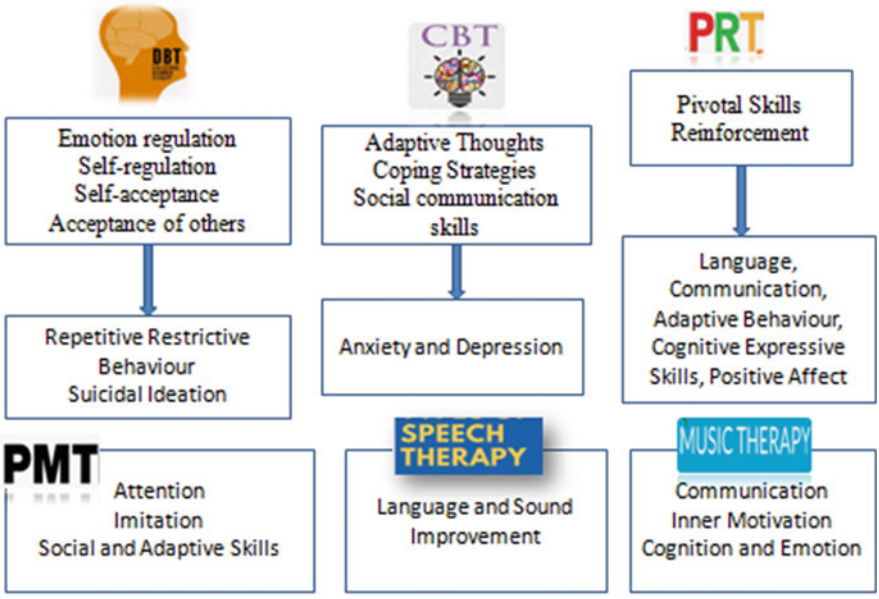

Fig. 15.2 Showing the rehabilitative techniques for autism spectrum disorder

ideation and attempts. Social anxiety is also a precursor for suicidal ideation. Therefore, DBT could be applied on them. This therapy is based on "dialectical therapeutic alliance" where the therapist teaches skills related to emotion regulation, self-regulation, self-acceptance and acceptance of other (Huntjens et al. 2020; Salsman and Linehan 2006). Learned emotion regulation reduces RRBs (repetitive restrictive behaviour) (Salsman and Linehan 2006). Current advances have proved the efficacy of DBT in reducing suicidal ideation. Through randomized single blind technique, it was found that DBT is effective in teaching emotion regulation that further decreases suicidal thoughts and attempts among patients with ASD (Huntjens et al. 2020). But the authors suggest conduction of empirical follow-up studies with repeated measure trials in case of such findings, which was the limitation of the above-mentioned study.

15.5.2 Cognitive Behaviour Therapy (CBT)

CBT is used to reduce the anxiety of ASD patients. Anxiety is seen as a comorbid symptom in ASD and observed since the conceptualization of the disorder 70 years ago till today (Uljarević et al. 2016). According to Özerk and Cardinal (2020), ASD is more commonly observed among pre-school and school-age children. The basic premise of CBT is that there is an association between the way we think (cognition) and the way we act (behaviour). Therefore, non-adaptive thoughts and coping strategies perpetuate negative affect like anxiety (Spain and Happe 2019). A large number of ASD patients are refereed for CBT sessions, but the effectiveness among ASD patients depends on building therapeutic alliance, which requires socio-communication characteristics of the patients. Since ASD children and adults have difficulty in socio-communicative skills and introspecting own thought, therefore, it is very difficult to develop alliance with them (Kinnaird et al. 2019). By and large, cotemporary research supports CBT as the most widely used psychoeducation intervention for anxiety reduction among school-age children with ASD (Hillman et al. 2020). On the contrary, very few studies have used CBT to alleviate the depression co-occurring with ASD in adults. Restrictive and repetitive behaviour and thinking cause depressive symptoms (Gotham et al. 2014). A pilot study with randomized controlled group design found low-intensity CBT as feasible and effective for alleviating severe depression of adults with ASD (Russell et al. 2020).

15.5.3 Pivotal Response Treatment (PRT) Approach

PRT is not an independent type of therapy, but it is a technique derived from applied behaviour analysis (ABA). The term "pivotal" in this technique refers to "the target skills which when successfully acquired can elicit more widespread positive clinical gains in the Childs' other domain of functioning" (Lei and Ventola 2017). PRT is widely in used to teach and improve cognitive and language skills of ASD children. It is a natural behavioural intervention that aims at the pivotal skills combined with

motivational reinforcement and is found to benefit most of the children with ASD (Verschuur et al. 2020; Koegel et al. 2016). It improves language, communication, maladaptive behaviour, cognitive expressive skills and positive affect and decreased social avoidance and repetitive vocalization (Verschuur et al. 2020; Fossum et al. 2018).

15.5.4 Sensory-Motor Training

Sensory-motor abnormalities particularly postural sway are the most visible features of some ASD children and adults, along with social communication and interaction deficit (Bruchhage et al. 2018; Lim et al. 2018; Mosconi and Sweeney 2015). Recently, poor postural control was found to be associated with poor somatosensory input in children with ASD (Bucci et al. 2018; Gouleme et al. 2017). Largely, the problem is found in the cerebellum which results in impaired integration of somatosensory input through functional neuroimaging (Bruchhage et al. 2018). Recent advances in this connection are aiming to decrease postural sway and postural control by using different sensory-motor training programs. Travers et al. (2013) conducted a study in which video games were implied in biofeedback techniques for balance postural training of such children. The results showed significant improvement postural sway and better postural stability. Caldani et al. (2020) have provided preliminary evidence by demonstrating positive impact of short-rehabilitation training program on postural control in children with ASD. The study consisted of 20 children in two groups—group 1 and group 2 (G1 & G2)—matched on age, IQ and sex. G1 was given short posture rehabilitation training, while G2 served as the control group. Their posture was measured two times, before training is given—time 1 (T1)—and after giving the training, time 2 (T2) They found that T1 measurement was the same in both the groups; however, at T2, postural control and stability improved in the treatment group (G1).

15.5.5 Parent-Mediated Intervention (PMI)

Parent-mediated training programmes are used for young children of ASD. Parents learn the therapy from therapists and provide support to their children, e.g. joint attention therapy, social communication therapy and behaviour therapy. Manoharan et al. (2019) studied the impact of Brief Parent-Mediated Intervention on joint attention, imitation and social and adaptive skills of children with ASD living in South India. They found that after 12 weeks of training, parents reported improvement on children's outcome measures as compared to the control group. This study suggested effectiveness of the parent-mediated intervention for attention, imitation and social adaptive skills. Despite documenting evidence on PMI outcomes, current studies suggest that parental characteristics play a crucial role in PMI outcome such as parental stress, socio-economic status and autism phenotype which are related to varying effects of PMI (Shalev et al. 2020).

15.5.6 Speech Therapy Intervention

Communication in inherent social behaviour and given the diagnosis of ASD, speech is a prominent disability. In addition to pharmacological treatment for language improvement, speech therapy is used to improve the language deficiency of ASD children and adolescents. Speech-related issues such as echolalia, improper use of pronouns, improper grammatical structure of sentence, etc. are commonly observed (Oliveria et al. 2018). Although language deficiency is the major symptom of ASD, ASD patients need SLPs—speech language pathologists. However, it has been found that SLPs are not regularly used in the routine assessment of the speech of these children (Hus 2017). Insufficient training in using language assessment tools is a probable reason (Gillon et al. 2017). Multidisciplinary approach is recommended for the assessment of ASD which includes the involvement of SLPs along with physical and mental health professionals (Volkmar et al. 2014).

15.5.7 Music Therapy (MT)

Conceptually defining the term, "music therapy" is considerably insoluble because this therapy involves interdisciplinary component "music" and "therapy" (Eren 2017). The American Music Therapy Association (AMTA) has defined it as "the clinical and evidence-based use of music interventions to accomplish individualized goals within a therapeutic relationship by a credentialed professional who has completed an approved music therapy program". There are a number of approaches to MT, e.g. Orff approach to music therapy (OMT), the Kodaly approach to music therapy (KMT), the Dalcroze approach to music therapy (DMT), Kindermusik and music therapy (KinMT), psychodynamic approach to music therapy (PMT), behavioural approach to music therapy (BMT), music therapy in wellness (MTW), neurologic music therapy (NMT), biomedical music therapy (BioMT), sensory integration approach to music therapy (SIMT), etc. (Eren 2017). But the profile study of most preferred and effective music therapy for children with ASD shows that behaviour approach and sensory integration approach are the most effective ones. It involves singing, bodily movement, dancing and communicating while listening to music (American Music Therapy Association 2005). Music therapy has always given encouraging results when employed to improve the physical, emotional, cognitive and social requirements of children with developmental disability. Findings of previous studies have mentioned the application of music therapy for children with ASD to facilitate a variety of skills such as communication, to maintain relationship with adults, increased inner motivation for mastery, etc. (Stevens and Clark 1969; Yinger and Gooding 2014). A recent study has tested the impact of active music therapy and passive music therapy among children with ASD. Bharathi et al. (2019) conducted an empirical study to examine the impact of active MT and passive MT on social skills of children with ASD in South India. Along with listening to music, the active MT group was required to dance, play music instrument and sing songs. However, the passive MT group listened to music

alone. Findings showed the former group scored high on perspective-taking ability, initiating interaction, responding to others while communicating, maintaining relationships and interaction. Therefore, it is suggested that MT has a significant influence on improving social skills of ASD children.

15.5.8 Sensory Integration Therapy

Sensory integration therapy is used as an occupational therapy to make children and adults with ASD learn the adaptive sensory and motor ability, according to the environmental demands. This therapy involves tasks which require sensory-motor coordination such as use of deep busing, bounce pads, scooter boards, weighted vest and clothing, etc. (Shaw 2002). A recent systematic review of those interventions shows limited efficacy (Bodison and Parham 2018). The impact of this kind of therapy shall be seen with the age-related perspective. For example, Ayres Sensory Integration (ASI) is found effective for children with ASD whose age ranges between 4 and 12 years (Schoen et al. 2019). ASI is a sensory integration intervention used for children, in which the therapist identifies the sensory-motor issue by using an assessment tool. These issues must interfere with the functional ability of the child at home and in school. After that, intervention is given largely through designing a play.

15.6 Conclusion

This chapter focuses on the cognitive impairment (i.e. social cognition, non-social cognition, language and speech impairment, intellectual impairment) and executive dysfunction and rehabilitation (i.e. dialectical behaviour therapy, cognitive behaviour therapy, pivotal response treatment approach, sensory-motor training, parent-mediated intervention, speech therapy intervention, music therapy and sensory integration therapy) aspects of children and adults with ASD. Findings of recent studies suggest that autism spectrum disorder is one of the most vulnerable disorders. The functional ability of ASD can be rehabilitated by means of various non-pharmacological interventions.

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