Chapter 1: Neurodegenerative disorder: Alzheimer's disease

1.1 Neurodegenerative disorders

Neurodegenerative disorders are incurable and debilitating conditions that result in progressive loss of nerve cells, mental functioning, and difficulty in movement. These are a serious threat to elderly human health. Neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), frontotemporal dementia (FTD) and spinocerebellar ataxia (SCA) [1]. These diseases are very diverse in their pathophysiology, with some affecting the cognitive functions while others are affecting a person's ability to move, speak and breathe [1].

1.1.1 Alzheimer's disease

German clinical psychiatrist and neuroanatomist Alois Alzheimer reported "A peculiar severe disease process of the cerebral cortex" to the 37th Meeting of South-West German Psychiatrists in Tubingen on 1906. Emil Kraepelin promptly included that case as 'Alzheimer's disease' in the 3rd edition of his text Psychiatrie in 1910 [2]. It is one of the most common neurodegenerative diseases and accounts for more than 80% of dementia cases worldwide in older adults. It leads to progressive mental, behavioral, functional decline and inability to learn. AD is primarily characterized by the progressive loss of memory associated with other cognitive deficits. The global burden of the population suffering from AD and other dementia was assessed 40·2–52·7 million in 2015 [3]. The two strong hypotheses concerning the pathogenesis of AD are based on the formation of senile plaques (SP) or neuritic plaques and neurofibrillary tangles (NFTs), which ravage the normal cognitive activity of the brain. One of the

hallmarks of AD is the accumulation of amyloid plaques between neurons in the brain. Beta-amyloid, a protein fragment, is snipped from an amyloid precursor protein (APP). In a healthy brain, these protein fragments are broken down and eliminated. In AD, the fragments accumulate to form hard, insoluble plaques. Another hallmark of AD is insoluble twisted fibers found inside the brain cells, known as NFTs. These primarily consist of a protein called tau, which forms part of a structure called a microtubule. The microtubule helps to transport nutrients and other essential substances from one part of the nerve cell to another. In AD, however, the tau protein is abnormal, and the microtubule structures collapse.

1.1.2 Parkinson's disease

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder affecting the older population [4]. There is loss of dopaminergic neurons from substantia nigra and development of neuronal Lewy bodies which lead to motor impairment in the disease [5], *i.e.*, tremors, rigidity and bradykinesia [6]. Thinking and behavioral problems, *i.e.,* dementia, depression, and anxiety become common in the advanced stages of PD.

1.1.3 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a rare, late-onset, fatal neurodegenerative disorder. It is characterized by progressive voluntary muscular paralysis resulting from degeneration of motor neurons from the primary motor cortex, corticospinal tracts, spinal cord and brain stem [7].

1.1.4 Huntington disease

Huntington disease (HD) is an inherited disease caused by progressive breakdown of nerve cells [8]. HD is caused by a mutated form of the huntingtin gene; where excessive (more than 36) CAG repeats result in formation of an unstable protein. These expanded

repeats lead to production of a huntingtin protein that contains an abnormally long polyglutamine tract at the N-terminus. At the cellular level, faulty huntingtin gene results in neuronal dysfunction and cell death through various mechanisms, *i.e.,* proteolysis, transcription, direct neurotoxicity and mitochondrial dysfunction [9]. Currently, there is no disease-modifying treatment for HD, but clinical developments in recent years have focused on supportive and symptomatic management [10].

1.1.5 Frontotemporal dementia

Frontotemporal dementia (FTD) encompasses six types of dementia, *i.e.,* behavioral variant of FTD, semantic variant primary progressive aphasia, nonfluent agrammatic variant primary progressive aphasia, corticobasal syndrome, progressive supranuclear palsy, and FTD associated with motor neuron disease [11]. It is second most common cause of dementia after AD. Currently, there is no approved drug for disease-modifying purpose; however, asymptomatic treatments through selective serotonin reuptake inhibitors and atypical antipsychotic agents are typically used [12].

1.2 Pathophysiology of Alzheimer's disease

The atrophy of cerebral cortex and loss of cortical and subcortical neurons are significant characteristics of the AD [13]. Amyloid plaques, insoluble aggregates of hydrophobic β-amyloid peptide and NFTs composed of hyperphosphorylated tau protein, are pathological markers of AD [14]. In healthy individuals also, small number of β-amyloid plaques and neurofibrillary tangles can be observed, but they are abundant in patients with AD [15]. In advanced cases of the disease, β-amyloid plaques and NFTs are numerous and most abundant in hippocampus and associative regions of the cortex [16]. In AD, there is marked deficiency of acetylcholine due to atrophy and degeneration of subcortical cholinergic neurons, mainly those present in basal forebrain,

that provides cholinergic innervation to the whole cerebral cortex [17]. The cortical and hippocampal targets, which receive cholinergic input, are also destructed [18]. The deficit is not only related to acetylcholine but also involves other neurotransmitters, including serotonin, glutamate, and neuropeptides, *etc.* [19].

1.2.1 Role of amyloid precursor protein

Amyloid precursor protein (APP) is a 770-amino acid membrane protein and is expressed by many cells, including CNS neurons. Its cleavage involves three proteases, *i.e.*, α-secretases, β-secretases, and γ-secretases. The cleavage by α-secretase produces soluble APP (sAPP), which is believed to have neurotropic and neuroprotective properties [20]. Aβ formation involves cleavage at two different points by β- and γ-secretases. The enzyme γ-secretase (large intramembrane complex of several proteins) lacks precision and cuts APP at different points generating Aβ fragments of different lengths, including $A\beta_{40}$ and $A\beta_{42}$ [21]. Mutations in this region of APP gene affect the preferred cleavage point and leads to overproduction of $A\beta_{42}$. Both proteins aggregate to form amyloid plaques, but $A\beta_{42}$ shows a stronger tendency to do so as compared to $A\beta_{40}$ and is mainly responsible for amyloid formation [22]. Mutations in presenilin genes result in increased γ-secretase activity, as presenilin proteins form part of γ-secretase complex. These mutations in AD increase the ratio of $A\beta_{42}$: $A\beta_{40}$ that can be detected in plasma and serves as a marker for the familial AD. Mutations in ApoE4 gene (for lipid transport protein) that facilitates the clearance of Aβ oligomers, also predispose to AD, because the mutant form of ApoE4 proteins is less efficient in this function [23].

1.2.2 Role of beta-secretase

Amyloid plaques, primarily composed of Aβ, progressively develop in the brain of AD patients, and mutations in three genes (APP, PS1, and PS2) cause early onset familial AD (FAD) by increasing synthesis of toxic $A\beta_{42}$ peptide [24]. Given the strong

association between Aβ and AD, therapeutic strategies to lower the concentration of Aβ in the brain should prove beneficial for the treatment of AD. Aβ is a proteolytic product of large Type I membrane protein, amyloid precursor protein (APP) [25]. Two proteases, termed as β- and γ-secretases, cleave APP to generate the Aβ peptide. The molecular identities of these proteases were unknown for over a decade. The γ-secretase has been tentatively identified as the presenilin proteins, PS1 and PS2, and β-secretase (BACE) is the novel transmembrane aspartic protease, β-site APP Cleaving Enzyme 1 (BACE1; also called Asp2 and memapsin 2) [26]. BACE 2, a novel protease homologous to BACE1, was also identified, and the two BACE enzymes define a new family of transmembrane aspartic proteases. BACE1 exhibits all the properties of β-secretase, and as the key enzyme that initiates the formation of Aβ and thus is an attractive drug target for AD [27].

1.2.3 Role of amyloid beta

Aggregation and accumulation of Aβ in the brain may result from increased production of Aβ, decreased degradation, or reduced clearance across the BBB. Aβ oligomers impair synaptic functions and related signaling pathways, changing neuronal activities, and trigger the release of neurotoxic mediators from glial cells [28]. Fibrillar amyloid plaques displace and distort neuronal processes. The lipid transport protein apoE4 impairs Aβ clearance and promotes Aβ deposition. When expressed within stressed neurons, apoE4 is cleaved into neurotoxic fragments that disrupt the cytoskeleton and impair mitochondrial functions.

1.2.4 Role of monoamine oxidase

Monoamine oxidase (MAO) exists in two isoenzymes, MAO-A and MAO-B; both are formed neurotoxic by-products, *i.e.*, hydrogen peroxide, toxic aldehydes, and hydroxyl free radicals. MAO-B has decreased the levels of the monoamines dopamine,

norepinephrine, and serotonin in the AD brains compared with healthy aging brain [29]. MAO-B up-regulates by 3-fold in the temporal and frontal cortex and associates with gliosis in AD, which can increase of H_2O_2 and oxidative free radicals [30].

1.2.5 Role of tau-tubulin kinase

Tau-tubulin kinase (TTBK), a serine/threonine and tyrosine kinase enzyme of casein kinase 1(CK-1) family, is involved in various physiological processes including mitosis, ciliogenesis, and neurotransmission, *etc*. The enzyme has two isoforms: TTBK1 and TTBK2. However, TTBK1, a neuron specific tau kinase, is responsible for phosphorylation of tau protein and paired helical filaments (PHFs) [31, 32]. The phosphorylations occur at residues Ser198, Ser199, Ser202, and Ser422, to assist tau aggregation and increase the formation of NFTs in AD [33].

1.2.6 Role of tau

Tau, which is usually most abundant in axons, becomes mislocalized to the neuronal soma and dendrites and forms inclusions called NFTs. The α-synuclein may also self-assemble into pathogenic oligomers and form larger aggregates (Lewy bodies). Both tau and α-synuclein can also be released into the extracellular space, where they may spread to other cells. Vascular abnormalities impair the supply of nutrients and removal of metabolic by-products, cause microinfarcts, and promote the activation of glial cells [20].

1.2.7 Acetylcholine

In attentional processing, acetylcholine (ACh) plays a major role. The area throughout the whole neocortex receive cholinergic inputs from basal forebrain, and thus, ACh function extends beyond attentional processing, and cholinergic signaling has an impact on cognition also [34]. The cholinergic hypothesis of AD states that cortical deficiencies in cholinergic neurotransmission contribute to the specific cognitive deficits seen in

patients; however, the extent to which it is directly related to cholinergic signaling is not clear [35]. In AD, the activity of choline acetyltransferase, the enzyme involved in ACh synthesis is reduced to $35 - 50\%$ of normal levels. Synaptic reuptake of choline is reduced to 60% (approximately) of normal levels in AD [36]. Direct measurement reveals that synthesis level of Ach is decreased by half in affected patients that can be correlated with increasing severity of dementia in AD patients [37].

1.2.8 Role of glutamate

The ability to think and remember is derived from various input and output pathways between hippocampus and neocortex. These pathways rely on signaling mediated by neurotransmitter glutamate [38]. In AD patients, there is a disruption in glutamatergic neurotransmission cycle at the glial cell reuptake of free glutamate from synapse. Neuropathological studies have shown decreased levels of glutamate reuptake in the frontal and temporal cortices of AD patients, possibly because of oxidative modification of the glutamate transporter 1 molecule [39]. Also, diminished uptake by vesicular glutamate transporter has been reported in AD patients. These neuropathological studies suggest the involvement of glutamatergic system in AD. As per the glutamatergic hypothesis, inefficient removal of free glutamate from synapse results in abnormally high levels of synaptic glutamate under resting conditions. Additionally, as the decrease in vesicular glutamate uptake causes less glutamate to be stored in each vesicle, neurons are left with fewer neurotransmitter molecules to release into the synaptic cleft at the time of neuronal activity [40].

1.2.9 Role of N-methyl-D-aspartate receptor

AD is characterized by loss of synapses, deposition of Aβ plaques, NFTs, and hyperphosphorylated tau [41]. These changes are associated with NMDARs activation and oxidative stress, which ultimately result in AD pathology. Further, Aβ also triggers

NMDA-mediated Ca^{2+} influx, excitotoxicity, and stress-related signaling pathways in neurons which may worsen aging-related increase in oxidative stress, impaired energy metabolism, and defective Ca^{2+} homeostasis [42]. N-methyl-D-aspartate receptors (NMDARs) are cationic channels gated by the neurotransmitter glutamate, which play an essential role in excitatory transmission, synaptic integration, learning and memory in the central nervous system CNS. NMDAR activation, excessive Ca^{2+} flux, and free radical generation are associated with synaptic dysfunction and tau phosphorylation [42]. Excessive amount of glutamate is associated with intense transient influx of Ca^{2+}, leading to mitochondrial functional impairment characterized by activation of permeability transition pores in the inner mitochondrial membrane, cytochrome c release and depletion of ATP, and simultaneous formation of ROS. Therefore, it is evident that normal NMDAR and synapse functions are necessary for learning and memory, and abnormalities in function of NMDAR and synapse may participate in pathogenesis of AD at synaptic level [40].

1.2.10 Role of neuropeptides

Several studies of neuropeptide abnormalities (**Table 1.1**) have also been reported in AD. The neuropeptides that are considered to be altered in AD include somatostatin, neuropeptide Y, corticotrophin-releasing factor, vasopressin, oxytocin, neurotensin, substance P, vasoactive intestinal peptide, β-endorphin, α-melanocyte stimulating hormone, cholecystokinin, and galanin [43, 44].

1.2.11 Neuroprotective role of estrogens in Alzheimer's disease

The occurrence of AD is significantly correlated with loss of estrogen in women after menopause. In a study using more than 5,000 brain samples, a significant increase of NFTs formation was observed in women compared to men [45]. This global change of AD pathology in women appears to be closely associated with greater cognitive loss in

comparison to that in men [46]. Recent results indicate that the decline of estrogen levels in the brain may make neurons more susceptible to age-related neurodegenerative processes, also suggesting the protective roles of estrogen against AD [47]. However, the clinical relevance of estrogen-based hormone replacement therapy for AD and cognitive aging remains undetermined. The pathophysiological pathways of AD are illustrated in **Figure 1.1**.

Table 1.1 Pathological factors involving neuropeptides in Alzheimer's disease

Neuropeptide	Normal brain	Alzheimer's disease brain
Somatostatin	High	Markedly reduced in all areas of cortex
Neuropeptide Y	High	Normal or slightly reduced in cerebral cortex
Corticotrophin-releasing factor	Low	Markedly reduced in all areas of cortex
Vasopressin	Low	Moderately reduced in hippocampus
Oxytocin	Low	Slightly increased in hippocampus
Neurotensin	Low	Normal in hippocampus, low in amygdala and septum
Substance P	Medium	Normal or moderately reduced in cerebral cortex
Vasoactive-intestinal peptide	High	Normal or slightly reduced in cerebral cortex
β-Endorphin	Low	Slightly reduced in cerebral cortex
α-Melanocyte-stimulating hormone	Medium	Reduced in all area of cerebral cortex
Cholecystokinin	High	Normal or slightly reduced in temporal lobe
Galanin	High	Normal or increased in cerebral cortex

1.3 Stages of Alzheimer's disease

1.3.1 Early stage

The initial stage of AD is often ignored by relatives, friends, and sometimes professionals as well, and by considering it as "old age," just a regular part of aging process. As the inception of disease is gradual, it is difficult to ascertain exactly when it begins [48]. The persons with early-stage AD may:

> ➢ have problems talking correctly (language problems)
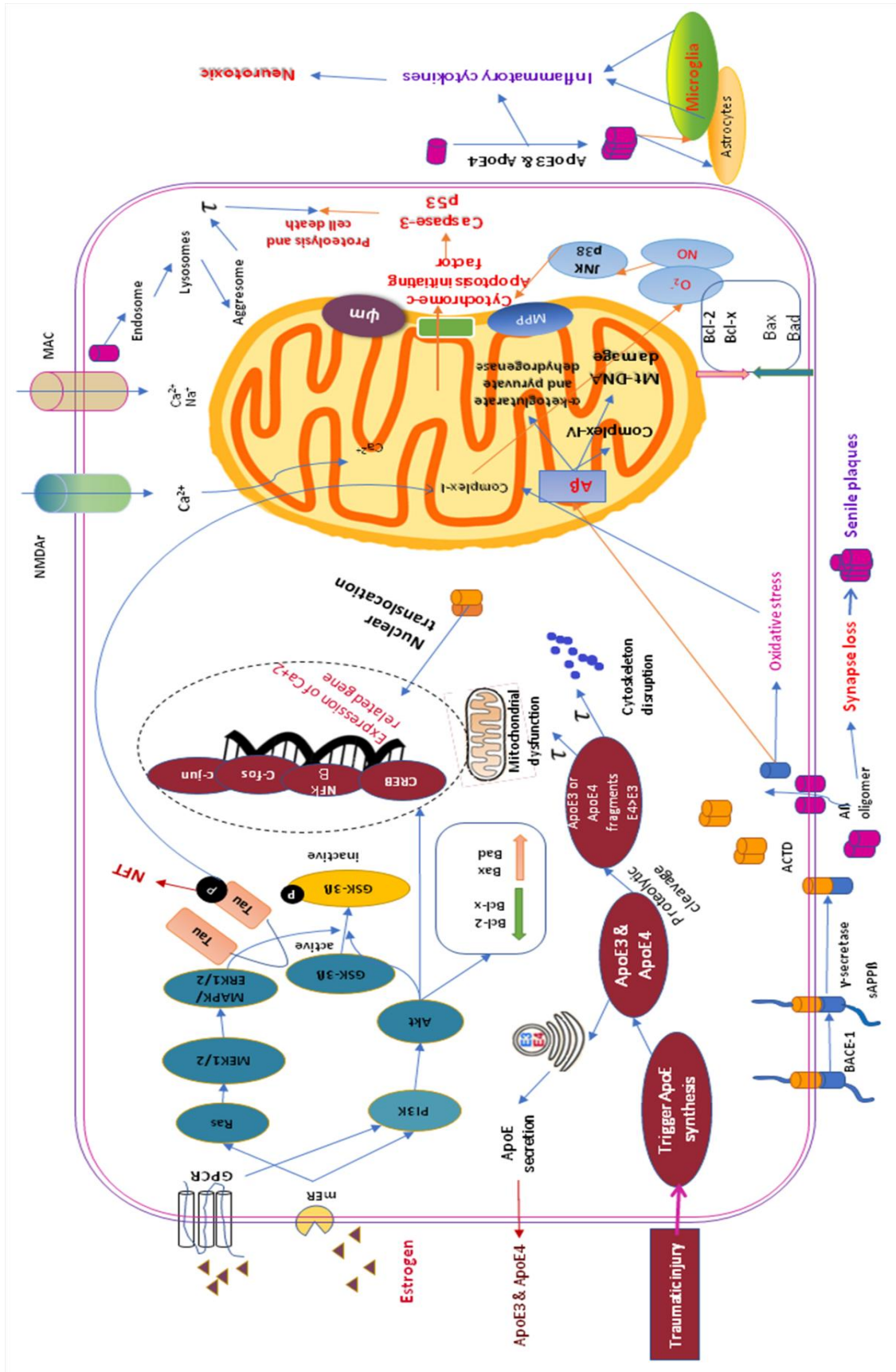
Figure 1.1 Pathophysiological pathways of Alzheimer's disease.

➢ have significant loss of memory mainly for things that have just happened

➢ not aware of the time of day or the day of the week

➢ become lost in familiar places

➢ have difficulty in decision making

➢ become inactive and unmotivated

➢ show mood changes, depression or anxiety

➢ react unusually or aggressively on occasions and loss of interest in activities

1.3.2 Middle stage

As the disease progresses, limitations become more explicit and restricting[49]. The person with dementia has difficulty with everyday living and:

➢ may become very forgetful, especially of recent events and people's name

➢ can no longer manage to live unaccompanied without problems

➢ is unable to cook, clean or shop

➢ may become hugely dependent on family members and caregivers

➢ need help with personal hygiene, *i.e.,* washing and dressing

➢ has increased difficulty with talking

➢ shows problems with wandering and other behavior such as repeated questioning and calling out, clinging and disturbed sleeping

➢ becomes lost at home as well as outside

➢ may have hallucinations

1.3.3 Late stage

The late stage is nearly total dependence and idleness. Memory disturbances become severe, and the physical side of the disease are more apparent. The person may:

➢ have difficulty in eating

➢ be incapable of communicating

- ➢ not recognize relatives, friends and familiar objects

- ➢ have trouble in understanding what is going on around them

- ➢ be unable to find his or her way around in the home

- ➢ have trouble in walking

- ➢ have difficulty in swallowing

- ➢ have bladder and bowel incontinence

- ➢ display inappropriate behavior in public

- ➢ be confined to a wheelchair or bed

1.4 Diagnosis of Alzheimer's disease

AD is diagnosed on the basis of the person's medical history, history from relatives, and behavioral observations, *i.e*., impaired memory or thinking (cognitive) skills, changes in personality or behaviors, inability to function in daily life, *etc*. The presence of characteristic neurological and neuropsychological features and the absence of alternative conditions are also very supportive in matching diagnosis of the disease [50, 51].

1.4.1 Assessing memory problems and other symptoms

Physicians may ask patient to answer questions or perform tasks associated with patient cognitive skills such as memory, abstract thinking, problem-solving, language usage, and related skills.

1.4.2 Laboratory tests

Laboratory tests are ruled out as other disorders also produce some symptoms similar to Alzheimer's dementia, *i.e*., thyroid disorder or vitamin B-12 deficiency *etc*.

1.4.3 Brain-imaging tests

Advanced medical imaging with computed tomography (CT) or magnetic resonance imaging (MRI), and with single-photon emission computed tomography (SPECT) or positron emission tomography (PET) can be applied to help exclude other cerebral pathology or subtypes of dementia [52]. CT scan uses X-rays to obtain cross-sectional images of the brain. MRI uses powerful radio waves and magnets to create a detailed view of the brain. PET scan uses a radioactive substance known as a tracer to detect substances in the body. The commonly used PET scan is a fluorodeoxyglucose (FDG) PET scan, which can identify brain regions with decreased glucose metabolism. The pattern of metabolism change can distinguish between different types of degenerative brain disease. PET scans have recently been developed that detect clusters of amyloid proteins (plaques), associated with Alzheimer's dementia, but this type of PET scan is typically used in the research setting.

1.5 Treatment of Alzheimer's disease

1.5.1 Pharmacological treatment

A significant treatment approach of AD involves the attempt to increase the cholinergic function of brain.

1.5.1.1 Precursors of acetylcholine synthesis

This was an early approach and involved use of choline chloride and phosphatidylcholine (lecithin), the precursors for synthesis of Acetylcholine (ACh), but they didn't show any clinically significant efficacy.

1.5.1.2   Cholinesterase inhibitors

Acetylcholinesterase (AChE) enzyme is responsible for the catabolism of ACh, physostigmine is a reversible AChE inhibitor, but its use is limited due to short half-life

and tendency to produce symptoms of systemic cholinergic excess at therapeutic doses [53]. Four AChE inhibitors, currently approved by the FDA, for treatment of AD are tacrine (now withdrawn), donepezil, rivastigmine, and galantamine. Tacrine is a potent centrally-acting inhibitor of AChE [54]. Its side effects are significant, dose-limiting and include abdominal cramping, anorexia, nausea, vomiting, diarrhea, and elevations of serum transaminases. Thus, it is not used often clinically. Donepezil is a selective inhibitor of AChE in the CNS and has little effect on AChE in peripheral tissues [54]. Rivastigmine and galantamine are dosed twice daily and produce similar degree of cognitive improvement. Adverse effects associated with donepezil, rivastigmine, and galantamine are like tacrine, but less frequent and severe and include nausea, diarrhea, vomiting, and insomnia [55]. Further, unlike tacrine, they are not associated with hepatotoxicity (**Figure 1.2**). Butyrylcholinesterase (BChE) has been noted to be increased significantly in the late stages of AD, thus making it also a feasible drug target [56]. Further experience with the dual AChE and BuChE enzyme inhibitors, may improve the treatment of AD [57].
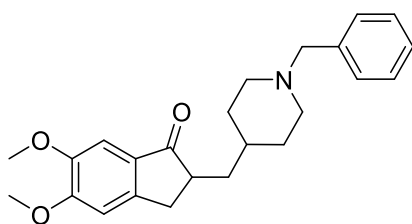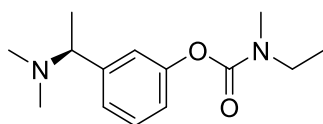

Donepezil (piperidine)
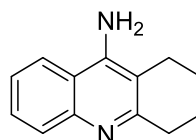Non-competitive and reversible inhibitor
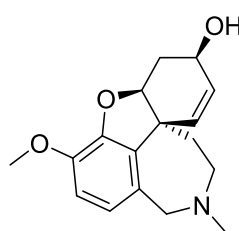
Galanthamine (tertiary alkaloid)
Reversible and competitive inhibitor

Rivastigmine (carbamate)
Non-competitive and reversible inhibitor

Tacrine (aminoacridine)
Mixed competitive/noncompetitive inhibitor

Figure 1.2 FDA approved AChE inhibitors for the treatment of Alzheimer's disease.

1.5.1.3   NMDA receptor antagonist

It is an alternative strategy for treatment of AD and includes the use of memantine [58]. It produces a dose-dependent blockade of NMDA receptors. Adverse effects of memantine are usually mild, reversible and may include headache or dizziness (**Figure 1.3**).
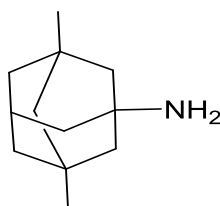
Memantine

Figure 1.3 NMDA receptor antagonist for the treatment of Alzheimer's disease.

1.5.1.4   Matrix metalloproteinases inhibitors

In normal human brain, the matrix metalloproteinases (MMPs) levels are quite low. However, it is reported to be upregulated during neurological disorders, including AD and after injuries. The altered MMPs expression in AD had been reported previously [59]. Brkie *et al.,* measured the expression of MMP gene in choroid plexus epithelial (CP) and cerebrospinal fluid (CSF) to establish a correlation between MMPs and Aβ induced blood-CSF barrier (BCSFB) leakage. An increase in MMPs activity was observed simultaneously in CSF with Aβ_{1-42} oligomer injection. Intracerebroventricular co-treatment of Aβ oligomers with GM6001, a non-selective MMP inhibitor, reduced the Aβ oligomer-mediated BCSFB disruption [60]. It was found that MMP-2 and 9 were engaged in different pathological cascade of AD [61]. The role of MMP-9 in Aβ promoted neurotoxicity in AD has not been understood completely [62].

1.5.2 Non-pharmacological therapy for AD

These therapies do not involve medication and are often used to maintain or improve cognitive function, the ability to perform activities of daily living or overall quality of

life. They may also be used to decrease behavioral symptoms like depression, apathy, wandering, sleep disturbances, agitation and aggression. The examples include computerized memory training, listening to favorite music as a way to stir recall, and incorporating special lighting to lessen sleep disorders. The non-pharmacologic therapies have not been shown to alter the course of AD, as with current pharmacologic therapies. The reviews and meta-analysis of non-pharmacologic therapies, tested in randomized controlled trials, have found that some are beneficial to people with Alzheimer's dementia. Among these are exercise and cognitive stimulation. A meta-analysis reported that aerobic exercise and a combination of aerobic and non-aerobic exercises could improve cognitive function. Further, systematic review found that exercise has a positive effect on overall cognitive function, some aspects of well-being and is associated with slower rate of cognitive decline in people with AD [63].

1.5.2.1   Vagus nerve stimulation

The basis behind effectiveness of vagus nerve stimulation (VNS), on cognition, is nucleus of solitary tract in the brain that is the central relay station for afferent vagal nerve fibers [64]. This nucleus has widespread projections to many areas in forebrain and brain stem including amygdala and hippocampus that are involved in learning and memory function [65]. VNS cause changes in electrophysiology and metabolic profile of these structures.

1.5.2.2   Deep brain stimulation

It is one of the neuromodulations approaches considered for AD. It modulates the activity of neural elements by implanted electrodes in a vital brain region with an internal pulse generator [66]. The use of deep brain stimulation (DBS) in AD is based on rationale that apart from neurodegenerative disorder, AD can also be considered as

neural circuit disorder because it affects several integrated cortical and subcortical pathways involved in memory and cognition [67].

1.6 References

[1] A.D. Gitler, P. Dhillon, J. Shorter, Neurodegenerative disease: models, mechanisms, and a new hope, in, *The Company of Biologists Ltd | Disease Models & Mechanisms* 10 (2017) 499–502.

[2] H. Hippius, G. Neundörfer, The discovery of Alzheimer's disease, *Dialogues in Clinical Neuroscience*, 5 (2003) 101–108.

[3] V.L. Feigin, A.A. Abajobir, K.H. Abate, F. Abd-Allah, A.M. Abdulle, S.F. Abera, G.Y. Abyu, M.B. Ahmed, A.N. Aichour, I. Aichour, Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015, *The Lancet Neurology*, 16 (2017) 877–897.

[4] C.M. Tanner, F. Kamel, G.W. Ross, J.A. Hoppin, S.M. Goldman, M. Korell, C. Marras, G.S. Bhudhikanok, M. Kasten, A.R. Chade, Rotenone, paraquat, and Parkinson's disease, *Environmental Health Perspectives*, 119 (2011) 866–872.

[5] E. Masliah, E. Rockenstein, I. Veinbergs, M. Mallory, M. Hashimoto, A. Takeda, Y. Sagara, A. Sisk, L. Mucke, Dopaminergic loss and inclusion body formation in α-synuclein mice: implications for neurodegenerative disorders, *Science*, 287 (2000) 1265–1269.

[6] J. Jankovic, Parkinson's disease: clinical features and diagnosis, *Journal of Neurology, Neurosurgery & Psychiatry,* 79 (2008) 368–376.

[7] L.C. Wijesekera, P. Nigel Leigh, Amyotrophic lateral sclerosis, *Orphanet Journal of Rare Diseases*, 4 (2009) 3.

[8] J.P. Vonsattel, R.H. Myers, T.J. Stevens, R.J. Ferrante, E.D. Bird, E.P. Richardson, Neuropathological classification of Huntington's disease, *Journal of Neuropathology & Experimental Neurology*, 44 (1985) 559–577.

[9] F.O. Walker, Huntington's disease, *The Lancet*, 369 (2007) 218–228.

[10] P. McColgan, S.J. Tabrizi, Huntington's disease: a clinical review, *European Journal of Neurology*, 25 (2017) 24–34.

[11] B. Englund, A. Brun, L. Gustafson, U. Passant, D. Mann, D. Neary, J. Snowden, Clinical and neuropathological criteria for frontotemporal dementia, *Journal of Neurology, Neurosurgery, and Psychiatry,* 57 (1994) 416–418.

[12] E. Ratnavalli, C. Brayne, K. Dawson, J. Hodges, The prevalence of frontotemporal dementia, *Neurology*, 58 (2002) 1615–1621.

[13] P.J. Whitehouse, D.L. Price, A.W. Clark, J.T. Coyle, M.R. DeLong, Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis, *Annals of Neurology*, 10 (1981) 122–126.

[14] C. Rochais, C.d. Lecoutey, F. Gaven, P. Giannoni, K. Hamidouche, D. Hedou, E. Dubost, D. Genest, S. Yahiaoui, T. Freret, Novel multitarget-directed ligands (MTDLs) with acetylcholinesterase (AChE) inhibitory and serotonergic subtype 4 receptor (5-HT4R) agonist activities as potential agents against Alzheimer's disease: the design of donecopride, *Journal of Medicinal Chemistry*, 58 (2015) 3172–3187.

[15] K. Shoghi-Jadid, G.W. Small, E.D. Agdeppa, V. Kepe, L.M. Ercoli, P. Siddarth, S. Read, N. Satyamurthy, A. Petric, S.-C. Huang, Localization of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients with Alzheimer disease, *The American Journal of Geriatric Psychiatry*, 10 (2002) 24–35.

[16] D.J. Selkoe, Alzheimer's disease: genes, proteins, and therapy, *Physiological Reviews,* 81 (2001) 741–766.

[17] D.E. Kuhl, S. Minoshima, J.A. Fessler, E. Ficaro, D. Wieland, R.A. Koeppe, K.A. Frey, N.L. Foster, *In vivo* mapping of cholinergic terminals in normal aging, Alzheimer's disease, and Parkinson's disease, *Annals of Neurology,* 40 (1996) 399–410.

[18] B.T. Hyman, G.W. Van Hoesen, A.R. Damasio, Alzheimer's disease: glutamate depletion in the hippocampal perforant pathway zone, *Annals of Neurology*, 22 (1987) 37–40.

[19] B.J. Everitt, T.W. Robbins, Central cholinergic systems and cognition, *Annual Review of Psychology*, 48 (1997) 649–684.

[20] C. Sturchler-Pierrat, D. Abramowski, M. Duke, K.-H. Wiederhold, C. Mistl, S. Rothacher, B. Ledermann, K. Bürki, P. Frey, P.A. Paganetti, Two amyloid precursor protein transgenic mouse models with Alzheimer disease-like pathology, *Proceedings of the National Academy of Sciences*, 94 (1997) 13287–13292.

[21] G. Thinakaran, E.H. Koo, Amyloid precursor protein trafficking, processing, and function, *Journal of Biological Chemistry*, 283 (2008) 29615–29619.

[22] M.P. Mattson, S.W. Barger, B. Cheng, I. Lieberburg, V.L. Smith-Swintosky, R.E. Rydel, β-Amyloid precursor protein metabolites and loss of neuronal Ca^{2+} homeostasis in Alzheimer's disease, Trends in Neurosciences, 16 (1993) 409–414.

[23] E. Karran, M. Mercken, B. De Strooper, The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics, *Nature Reviews Drug Discovery*, 10 (2011) 698–712.

[24] R. Vassar, D.M. Kovacs, R. Yan, P.C. Wong, The β-secretase enzyme BACE in health and Alzheimer's disease: regulation, cell biology, function, and therapeutic potential, *Journal of Neuroscience*, 29 (2009) 12787–12794.

[25] F. Kamenetz, T. Tomita, H. Hsieh, G. Seabrook, D. Borchelt, T. Iwatsubo, S. Sisodia, R. Malinow, APP processing and synaptic function, *Neuron*, 37 (2003) 925–937.

[26] S.H. Pasternak, J.W. Callahan, D.J. Mahuran, The role of the endosomal/lysosomal system in amyloid-beta production and the pathophysiology of Alzheimer's disease: reexamining the spatial paradox from a lysosomal perspective, *Journal of Alzheimer's Disease*, 6 (2004) 53–65.

[27] S.L. Roberds, J. Anderson, G. Basi, M.J. Bienkowski, D.G. Branstetter, K.S. Chen, S. Freedman, N.L. Frigon, D. Games, K. Hu, BACE knockout mice are healthy despite lacking the primary β-secretase activity in brain: implications for Alzheimer's disease therapeutics, *Human Molecular Genetics*, 10 (2001) 1317–1324.

[28] D.A. Butterfield, J. Drake, C. Pocernich, A. Castegna, Evidence of oxidative damage in Alzheimer's disease brain: central role for amyloid β-peptide, *Trends in Molecular Medicine*, 7 (2001) 548–554.

[29] R. Adolfsson, C. Gottfries, B. Roos, B. Winblad, Changes in the brain catecholamines in patients with dementia of Alzheimer type, *The British Journal of Psychiatry*, 135 (1979) 216–223.

[30] J. Saura, J. Luque, A. Cesura, M. Da Prada, V. Chan-Palay, G. Huber, J. Löffler, J. Richards, Increased monoamine oxidase B activity in plaque-associated astrocytes of Alzheimer brains revealed by quantitative enzyme radioautography, *Neuroscience*, 62 (1994) 15–30.

[31] S. Sato, R.L. Cerny, J.L. Buescher, T. Ikezu, Tau-tubulin kinase 1 (TTBK1), a neuron-specific tau kinase candidate, is involved in tau phosphorylation and aggregation, *Journal of Neurochemistry*, 98 (2006) 1573–1584.

[32] H. Lund, R.F. Cowburn, E. Gustafsson, K. Strömberg, A. Svensson, L. Dahllund, D. Malinowsky, D. Sunnemark, Tau-Tubulin Kinase 1 Expression, Phosphorylation and Co-Localization with Phospho-Ser422 Tau in the Alzheimer's Disease Brain, *Brain Pathology*, 23 (2013) 378–389.

[33] J. Xu, S. Sato, S. Okuyama, R.J. Swan, M.T. Jacobsen, E. Strunk, T. Ikezu, Tau-tubulin kinase 1 enhances prefibrillar tau aggregation and motor neuron degeneration in P301L FTDP-17 tau-mutant mice, *The FASEB Journal*, 24 (2010) 2904–2915.

[34] P.T. Francis, A.M. Palmer, M. Snape, G.K. Wilcock, The cholinergic hypothesis of Alzheimer's disease: a review of progress, *Journal of Neurology, Neurosurgery & Psychiatry*, 66 (1999) 137–147.

[35] J.L. Cummings, H.V. Vinters, G.M. Cole, Z.S. Khachaturian, Alzheimer's disease Etiologies, pathophysiology, cognitive reserve, and treatment opportunities, *Neurology*, 51 (1998) S2–S17.

[36] T. H Ferreira-Vieira, I. M Guimaraes, F. R Silva, F. M Ribeiro, Alzheimer's disease: targeting the cholinergic system, *Current Neuropharmacology*, 14 (2016) 101–115.

[37] E.J. Mufson, S.E. Counts, S.E. Perez, S.D. Ginsberg, Cholinergic system during the progression of Alzheimer's disease: therapeutic implications, *Expert Review of Neurotherapeutics*, 8 (2008) 1703–1718.

[38] N.C. Danbolt, Glutamate uptake, *Progress in Neurobiology*, 65 (2001) 1-105.

[39] C.M. Lauderback, J.M. Hackett, F.F. Huang, J.N. Keller, L.I. Szweda, W.R. Markesbery, D.A. Butterfield, The glial glutamate transporter, GLT-1, is oxidatively modified by 4-hydroxy-2-nonenal in the Alzheimer's disease brain: the role of Aβ1–42, *Journal of Neurochemistry*, 78 (2001) 413–416.

[40] J.T. Greenamyre, W.F. Maragos, R.L. Albin, J.B. Penney, A.B. Young, Glutamate transmission and toxicity in Alzheimer's *disease, Progress in Neuro-Psychopharmacology & Biological Psychiatry,* 12(4) (1988) 421–30.

[41] W. Danysz, C.G. Parsons, The NMDA receptor antagonist memantine as a symptomatological and neuroprotective treatment for Alzheimer's disease: preclinical evidence, *International Journal of Geriatric Psychiatry*, 18 (2003) S23–32.

[42] J.T. Greenamyre, A.B. Young, Excitatory amino acids and Alzheimer's disease, *Neurobiology of Aging*, 10 (1989) 593–602.

[43] D.J. Selkoe, The molecular pathology of Alzheimer's disease, *Neuron*, 6 (1991) 487–498.

[44] M.C. de Lacoste, C.L. White III, The role of cortical connectivity in Alzheimer's disease pathogenesis: a review and model system, *Neurobiology of Aging*, 14 (1993) 1–16.

[45] P.S. Green, K.E. Gridley, N.C. de Fiebre, Role of estrogen replacement therapy in memory enhancement and the prevention of neuronal loss associated with Alzheimer's disease, *The American Journal of Medicine*, 103 (1997) 19S–25S.

[46] J.W. Simpkins, M. Singh, J. Bishop, The potential role for estrogen replacement therapy in the treatment of the cognitive decline and neurodegeneration associated with Alzheimer's disease, *Neurobiology of Aging*, 15 Suppl 2 (1994) S195–S207.

[47] R.D. Brinton, Cellular and molecular mechanisms of estrogen regulation of memory function and neuroprotection against Alzheimer's disease: recent insights and remaining challenges, *Learning & Memory*, 8 (2001) 121–133.

[48] J.C. Morris, J.L. Price, Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease, Journal *of Molecular Neuroscience*, 17 (2001) 101–118

[49] G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price, E.M. Stadlan, Clinical diagnosis of Alzheimer's disease Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease, *Neurology*, 34 (1984) 939–939.

[50] X.Q. Che, N. Song, Y. Gao, R. Ren, G. Wang, Precision medicine of frontotemporal dementia: from genotype to phenotype, *Frontiers in Bioscience, Landmark*, 23 (2018) 1144–1165.

[51] H.-W. Klafki, M. Staufenbiel, J. Kornhuber, J. Wiltfang, Therapeutic approaches to Alzheimer's disease, *Brain*, 129 (2006) 2840–2855.

[52] M.L. Schroeter, T. Stein, N. Maslowski, J. Neumann, Neural correlates of Alzheimer's disease and mild cognitive impairment: a systematic and quantitative meta-analysis involving 1351 patients, *Neuroimage*, 47 (2009) 1196–1206.

[53] J.S. Birks, Cholinesterase inhibitors for Alzheimer's disease, *Cochrane database of systematic reviews*, 1 (2006), DOI: 10.1002/14651858.CD005593.

[54] A. Nordberg, A.L. Svensson, Cholinesterase inhibitors in the treatment of Alzheimer's disease, *Drug Safety*, 19 (1998) 465–480.

[55] P. Anand, B. Singh, A review on cholinesterase inhibitors for Alzheimer's disease, *Archives of Pharmacal Research*, 36 (2013) 375–399.

[56] A. Kumar, F. Pintus, A. Di Petrillo, R. Medda, P. Caria, M.J. Matos, D. Viña, E. Pieroni, F. Delogu, B. Era, Novel 2-pheynlbenzofuran derivatives as selective butyrylcholinesterase inhibitors for Alzheimer's disease, *Scientific Reports*, 8 (2018) 4424.

[57] N.H. Greig, D.K. Lahiri, K. Sambamurti, Butyrylcholinesterase: an important new target in Alzheimer's disease therapy, *International Psychogeriatrics*, 14 (2002) 77–91.

[58] C. Vasquez, K. Rao, G. Britton, NMDA Receptor Antagonist In Alzheimer's Disease Treatment: More Options Than Memantine?: Tu04-21, *Journal of Neurochemistry*, 118 (2011) 140–141.

[59] V.W. Yong, P.A. Forsyth, R. Bell, C.A. Krekoski, D.R. Edwards, Matrix metalloproteinases and diseases of the CNS, *Trends in Neurosciences*, 21 (1998) 75–80.

[60] M. Brkic, S. Balusu, E. Van Wonterghem, N. Gorlé, I. Benilova, A. Kremer, I. Van Hove, L. Moons, B. De Strooper, S. Kanazir, Amyloid β Oligomers Disrupt Blood–CSF Barrier Integrity by Activating Matrix Metalloproteinases, *The Journal of Neuroscience*, 35 (2015) 12766–12778.

[61] C. Saravanan, S.K. Singh, Status of research on MMPs in India, *Expert Opinion on Therapeutic Targets*, 15 (2011) 715–728.

[62] D. Kumar, M. Kumar, C. Saravanan, S.K. Singh, Curcumin: a potential candidate for matrix metalloproteinase inhibitors, *Expert Opinion on Therapeutic Targets*, 16 (2012) 959–972.

[63] T. Asada, Non-pharmacological therapy for Alzheimer's disease, Nihon rinsho. *Japanese Journal of Clinical Medicine*, 62 (2004) 72–75.

[64] M.J. Sjögren, P.T. Hellström, M.A. Jonsson, M. Runnerstam, H.C. Silander, E. Ben-Menachem, Cognition-enhancing effect of vagus nerve stimulation in patients with Alzheimer's disease: A pilot study, *The Journal of Clinical Psychiatry*, 63(11 (2002) 972-980.

[65] D.A. Groves, V.J. Brown, Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects, *Neuroscience & Biobehavioral Reviews*, 29 (2005) 493–500.

[66] A.W. Laxton, D.F. Tang-Wai, M.P. McAndrews, D. Zumsteg, R. Wennberg, R. Keren, J. Wherrett, G. Naglie, C. Hamani, G.S. Smith, A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease, *Annals of Neurology*, 68 (2010) 521–534.

[67] G.S. Smith, A.W. Laxton, D.F. Tang-Wai, M.P. McAndrews, A.O. Diaconescu, C.I. Workman, A.M. Lozano, Increased cerebral metabolism after 1 year of deep brain stimulation in Alzheimer disease, *Archives of Neurology*, 69 (2012) 1141–1148.

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