Review

Current Therapeutic Targets for Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is one of the most common multifactorial diseases, including a range of abnormal cellular/molecular processes occurring in different regions of the brain. This disease is considered to be a major contributor to dementia in the elderly people. The pathophysiology involves accumulation of extracellular plaques containing the β-amyloid protein which is generated by the breakdown of the β-amyloid precursor protein (APP) in the brain. Another mechanism involves formation of intracellular neurofibrillary tangles of hyperphosphorylated tau protein. The AD can be classified into two types, familial AD (FAD) and sporadic AD (SAD) based on heritability apart from this the early-onset AD (EOAD) and late-onset AD (LOAD) forms are based on the age of onset. Some proteins, such as APOE, APP, BACE (b-amyloid cleaving enzyme), secretases, PS1/2 and tau proteins are reported in AD brain and have been correlated with disease. It is still unclear whether this disease comprises genetic or environmental factors or both. Many palliative drugs are available for the disease but there is still thirst for curative drugs with greater efficacy. It is required to understand the key factors involved in disease progression and their suitability as drug targets for discovering new drugs against Alzheimer's disease. Main purpose of this review is to highlight the potential targets for Alzheimer's disease that have been studied in recent years.

Key words: Alzheimer's disease, Targets, Dementia, β-amyloid protein, Amyloid precursor protein, Genes.

Introduction

Today around 47 million people survive with dementia, globally. This number is projected to increase to more than 131 million by 2050 [1]. About 2.1 million Alzheimer's patients having age of 85 years or older were reported in year 2017[2]. Alzheimer's disease (AD) is one of the most common neurodegenerative disorders that causes dementia and it is characterized by amyloid deposition of a 39-42 AA peptide (Aβ) processed from the amyloid precursor protein (APP) and NFT. Genetic effects of APP and PSEN1/2 are also responsible for progression of the disease [3, 4, 5, 6] (Figure 1, 2). More than 95% cases of the AD are sporadic, where older age, low education degree, hypertension, hyperlipidaemia, heart disease; apolipoprotein E (ApoE) 4 allele polymorphism and diabetes are among the main factors responsible for the development of the disease. According to "amyloid cascade hypothesis" when processing of APP by β

and γ-secretase forms Aβ40 and Aβ42 peptides which further undergo aggregation and oligomer formation and finally cause formation of Amyloid plaques. [7, 8].

Alzheimer's Drug Targets

Currently many targets are being considered for anti-Alzheimer's drug discovery. Some of these drug targets are already having known inhibitors while others are still being studied for designing suitable ligands against them. Such targets have been described in Table 1 along with their sources and known function.

β-Secretase: Aspartyl Proteases(BACE)

BACE is a novel target having 501 amino acids, a type 1 transmembrane aspartic protease, related to the pepsin and retroviral aspartic protease families. BACE is known to have highest expression level in human brain. BACE antisense oligonucleotide treatment to

APP overexpressing cells is reportedly responsible for decreased production of β -secretase cleaved APP fragments. Recent studies suggest that levels of BACE1 protein and their activity was raised to approximately double in AD patient where BACE1 might initiate or enhance AD pathogenesis. The enzyme's key role in generation of Aβ, which is a major component of APP metabolism makes it popular target for drug development [9, 10, 11, 12, 13, 14].

γ-Secretase: Presenilin I

γ-Secretase complex has 170kDa MW with an additional 30-70kDa MW derived from nicastrin glycosylation [15] reaching up to total size 230kDa with 19 TMs (Transmembrane-segment) that belong to the family of intramembrane cleaving protease, consist of Aspartyl protease, Zinc mettaloprotease site-2 protease family and serine protease. γ-Secretases are multi-subunit enzyme complexes having proteolytic activity and play a vital role in generation of Aβ [16,17].

Butyrylcholinesterase (BuChE)

Butyrylcholinesterase (BuChE) is a hydrolase which is responsible for hydrolysing esters of choline [18]. Degeneration of basal forebrain cholinergic system is an indication of the AD [19,20]. Studies have found that BuchE biochemical properties were changed in the neurodegenerative disease like in AD. Due to loss of neurons Ach and AchE levels expressed in the high amount which was responsible for the
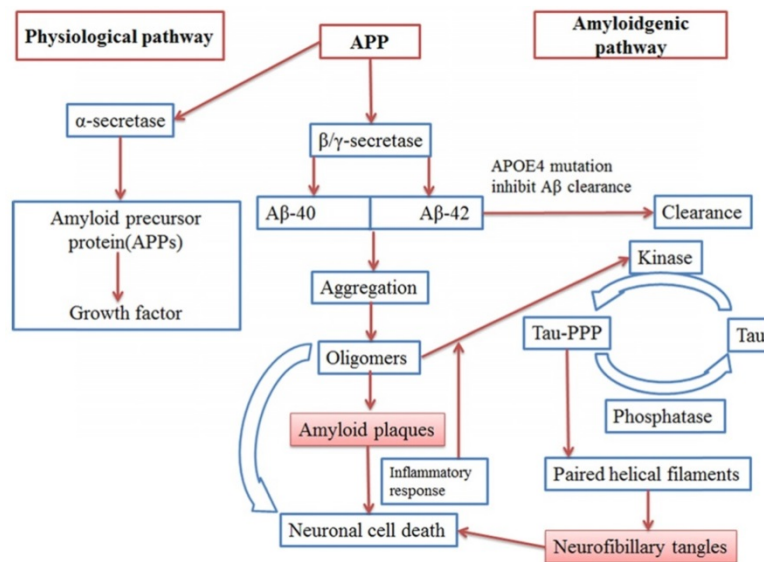

Figure 1: Hypothetical model of AD pathophysiology (Pathophysiological pathway and Amyloidgenic pathway)
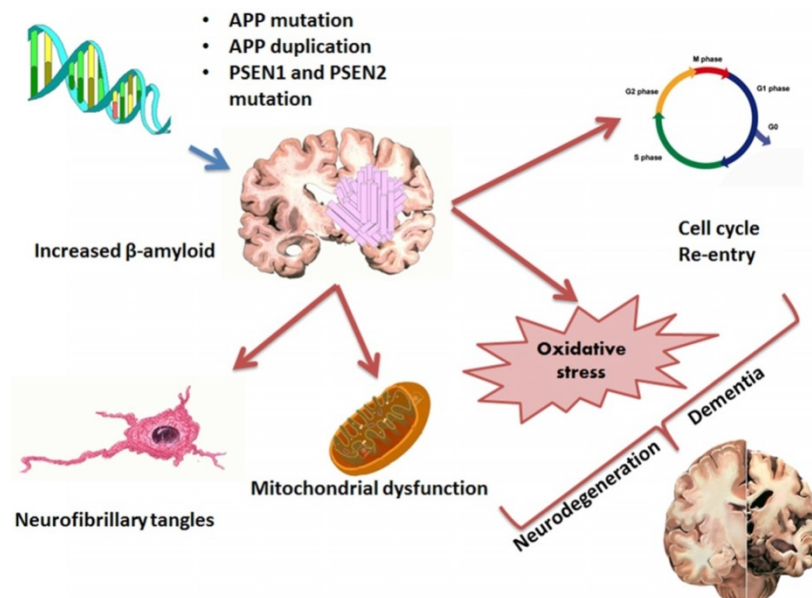

Figure 2: Pathophysiology and factors (Mutations, NFT, Oxidative stress, mitochondrial dysfunction) involved in AD

reduction of neurotransmitter and its enzyme [21, 22,23]. In cortical region BuchE level is increased during AD which is responsible for neuritic plaques and neurofibrillary tangle formation [19,24,25, 26,27,28,29].

Calcium-permeable AMPA receptors (CP-AMPARs)

AMPAR refers to one of the fastest excitatory neurotransmitters in the Central nervous system that are related to ionotropic glutamate receptors. It is involved in regulation of CP-AMARs in electrophysically produced synaptic plasticity and could be a therapeutic target for AD patients and other neurodegenerative disease. During Long-term potentiation (LTP) induction CP-AMPARs are employed from perisynaptic pools to contribute boosting synaptic $Ca2+$. [23].

Some researches suggests that CP-AMPAR is involved in the onset of synaptic pathology and formation of AMPAR and thus it is a therapeutic target for Alzheimer disease and other neurodegenerative Disease [30,31,32,33].

Calcitonin gene- regulated peptide (CGRP)

CGRP plays an important role as a potent vasodilator. It is known as a neurotransmitter in the Central nervous system [34] which contains 37 amino acids. It is distributed in different parts of the brain like hypothalamus, ventromedial nucleus of the thalamus, amygdala, grey matter, hippocampus and denate gyrate [35]. CGRP also helps in improving learning and memory processing [36].

Phosphodisterase (PDE)

PDE consist of a group of enzymes which control the rate of cAMP and cGMP hydrolysis and also contain 11 types of protein family members [37]. In brain regions like hippocampus, cortex stratium PDE isoforms play a crucial role in hydrolysis of cGMP [38,39,40,41,42,43,44] and intracellular signalling cascades. Studies suggest PDE2A, PDE5 as well as PDE9 are involved in memory formation [45, 43, 46, 47,48,49,50, 51, 52].

Muscarinic acetylcholine receptor (mAchR)

Muscarinic acetylcholine receptors (mAchR) belong to G-protein coupled muscarinic family and have some important functions like central cholinergic transmission learning and memory process [53,54]. M1 type of mAchR stimulates dephosphorylation of tau in PC12 cells which is responsible for alteration of hyperphosphorylation of tau protein and NFT pathology [55]. mAchR subtypes facilitate a variety of presynaptic and postsynaptic actions in hippocampus regions. In the hippocampus,

presynaptic mAchRs reduces excitatory and inhibitory responses [56, 57, 58] and some studies suggest that different subtypes inhibit Aspartate, glutamate, g-Ambiobutyric acid and Acetylcholine [59]. Autoreceptors like M2, M2-cardiaclike and M2-non-cardiac like and M4 [60] [61] inhibit the Ach release in hippocampus [62, 63]. M1, M2 and M4 proteins are also found in forebrain region in case of AD patient [64]. M1 and M2 also play an important role in learning and memory process in other brain regions [65, 66, 67].

Dopamine 2 receptor

Dopamine 2 receptor belongs to GPCR family, involved in neural signaling that trigger many important behavioural processes. Dopamine which acts as major neurotransmitter is released by dopaminergic neurons to govern movement, cognition, and emotion in CNS. Studies performed on AD mouse model suggest that Levodopa, a chemical that is converted into dopamine in body, has protective effect in learning and memory process and also reduced Aβ plaques number and size [68, 69, 70].

Gama aminobutyric Acid A receptor (GABA)

In human nervous system (mainly CNS), GABA plays a crucial role as inhibitory neurotransmitter. GABA receptor directly act on membrane potentials via ionic, control short and long term neuronal activity, synaptic plasticity and network plasticity [71, 72, 73, 74, 75]. GABA and small proportion of somatostatin are used as a neurotransmitter in cerebral cortex [76]. Some evidence show that in post-mortem brain, GABA concentration declined in temporal, frontal and occipital lobes [77, 78, 79].

Nuclear factor E2 related factor-2 (Nrf$_2$)

Nrf2 refers to a transcriptional activator of cell protection genes which also acts a therapeutic target for the treatment of neurodegenerative diseases including AD. Nrf2 targets contain cellular defence genes having drug metabolising enzymes, antioxidant response elements, DNA repair enzymes, molecular chaperons and proteasome subunits. These genes are involved in maintaining cellular redox balance and eliminating damaged proteins. Cellular stresses like oxidative damage was reportedly increased in case of AD [80,81]. Few studies suggest that xenobiotic metabolism is reduced in AD patients as well as APP/PS1 mutant mouse models [82,83]. Over expression of Nrf2 also protects against toxicity produced by Aβ 42 peptide in AD patients [84,85]. Nrf2 activity is regulated by Keap and GSK-3. Further GSK-3 plays a role in the pathogenesis of AD [86,87].

Gamma-secretase metabotropic glutamate receptor

Glutamate is known as primary excitatory neurotransmitter found in brain which activates G protein-coupled metabotropic glutamate receptors and ionotropic glutamate receptors [88]. Disruption in normal mGlu5 signalling is responsible for several neurodegenerative diseases like AD, Parkinson and Huntington disease [89,90]. mGluR5 binds to the heterotrimeric G-protein Gαq/11, which triggers phospholipase-C resulting in increased inositol-1,4,5 triphosphate formation and releasing of ca2+ from intracellular vesicles [91]. Studies suggest that mGluR5 also acts as receptor for Aβ42 and cellular prion protein (PrPc) [92,93,94,95,96,97].

N-myc downstream-regulated gene 2 (NDRG2)

N-myc downstream- regulated gene 2 is a family of genes having several functions like having role in differentiation, cell proliferation, and cell apoptosis. The NDRG comprises four members NDRG1-NDRG4. It has been observed that NDRG2 upregulation in AD models is involved in aging of brain [98, 99].

Serotonin 5-HT₆ receptor

Serotonin 5HT6 was discovered in 1993 and studies suggest that 5-HT6 receptor has a crucial role in the targeting AD by improving cognition dysfunction, synaptic plasticity, neurogenesis and survival of neurons in adult brain. In AD patient 5HT6 receptor showed significant reduction in cortical areas. Blockage of 5-HT6 receptor induced acetylcholine release and also affects Gabaergic and Glutamergic systems. Further, it has also been found that dysregulation of the 5-HT6 receptor in temporal cortex may be associated with behavioural symptoms in AD [100,101].

Protein tyrosine phosphatase 1B (PTP1B)

PTP1B belongs to phosphatases involved in the relevant modulation of signalling pathways triggered by the initiation of the tyrosine kinase receptor family [102]. Studies suggested that PTP1B is involved in many important functions like learning, memory, endoplasmic reticulum, stress, regulation of synapse dynamics and microglial mediated neuroinflammation [103,104, 105,106;107]. Higher expression of PTP1B is observed in hippocampal microglial regions and it is involved positive regulation of neuroinflammation [108].

Monoamine oxidase B (MAO-B)

MAO is the type of enzyme found in an outer layer of mitochondrial membrane and plays a key role in the metabolism of monoamine neurotransmitter [109,110]. MAO-B has been reported in the pathogenesis of AD in the astrogila region. Upregulation of MAO-B is also responsible for the production of Reactive oxygen species (ROS) and H_2O_2 which leads to AD pathology [111]. MAO has two isoforms MAO-A and MAO-B [112]. Studies suggested that MAO-B expression is increased in different regions like the hippocampus, cerebral cortex and astrocyte contribute to the AD.

NAD(P)H Quinone oxidoreductase 1 (NQO1)

NAD(P)H Quinone oxidoreductase 1 is a type of redox regulated flavoenzyme which is also known as cytosolic homodimeric flavoprotein. It plays an important role in monitoring cellular redox state. NQO1 triggers two electron reductions of quinones and related molecule aimed to enhance their solubility and excretion. Reports suggest that NQO1 is involved in maintaining oxidative stress, abnormality in redox balance in AD patient [113; 114]. NQO1 could be a novel therapeutic target for the AD.

Neurotrophic Receptor Tyrosine Kinase 1 (NTRK1)

NTRK1 receptors are produced by NTRK1 gene which belong to the family of nerve growth factor receptors that contain neurotrophin as a ligand. Neurotrophin helps in regulation and development of CNS and PNS [115,116,117].Expression of NGF receptors of NGF receptors p75 (NTR) and TrkA occur in basal forebrain nucleus basalis (NB) which is responsible for the promotion of cell survival. These cells are degraded in the AD [118,119,120,53,121, 122,123].

Amyloid protein precursor (APP)

Human APP gene was first discovered in 1987 from β-amyloid [124] and the gene was mapped to chromosome 21 [125,126]. APP belongs to membrane proteins containing extracellular domain and short cytoplasmic region. APP releases Aβ by two cleavage processes, one in the extracellular domain (β-secretase cleavage) and another one in the transmembrane region (γ-secretase cleavage). Different types of APP proteins can be formed by alternative splicing from the single gene. APP695 is a major splice form in neurons [127]. APP is cleaved by two different proteolytic pathways, one is a non-Amyloidogenic and other one is Amyloidogenic pathway. For this process, two main enzymes γ-secretase and β-secretase are responsible [128,129,130] (Figure 3).

Peroxisome proliferator activated receptor-γ(PPARs)

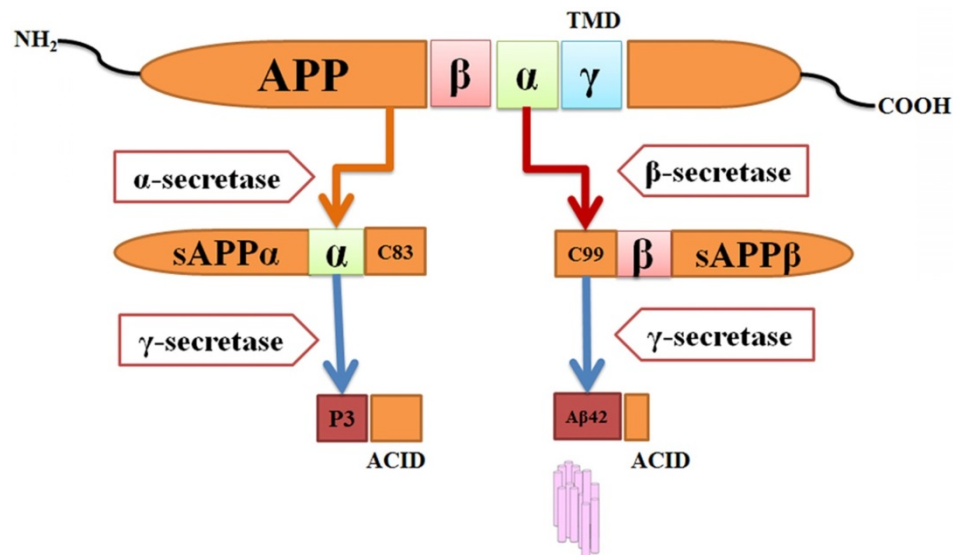PPARs consist of nuclear hormone receptors that

Figure 3: Amyloidgenic process of APP hypothesis and formation of Aβ-42. APP protein can be processed by different enzymes like β-secretase, γ- secretase and α- secretase. sAPPβ and sAPPα is produced with peptides C83 and C99.

contain 48 human ligand inducible transcription factors. Their activity is regulated by lipid metabolites and steroids [131]. PPARs have three types of receptors PPAR-α, PPAR-β and PPAR-γ. PPARs are involved in many functions like lipid storage, adipocyte differentiation, lipid storage and glucose homeostasis in many organs like brain, adipose tissue, placenta and skin [132].Studies suggested that PPARs show a wide range of effect in AD pathophysiology through several animal models. PPAR- γ activation leads to an increase in APOE and ABCA1 levels in astrocytes and microglial cells [133,134,135,136,137, 138,139,140,141,142,143].

C-C chemokine receptor type-5

Chemokines belong to an expanding family of cytokines a(CXC), b(CC), g(C) and (CX3C) that are involved in the recruitment of leukocytes to inflammatory sites. Previous studies suggest that interleukin (IL-8) receptor B is found in cortical neurons, hippocampal and in neuritic plaques of AD brains [144,145,146,147,148,149,150].

Nicotinergic acetylcholine receptor (nAChR)

nAChRs, which belong to ligand-gated ion channels, comprise of five subunits. Higher expression of it's α-subunit is found in brain regions related to cognitive, memory function. nAChR is also involved in the progression of sensory information which shows the involvement of nAChr in the AD [151,152]. Some studies suggest that β-amyloid is responsible for triggering tau phosphorylation via several signalling pathways, free radical formation, lipid peroxidation, cell membrane damage and oxidative stress (153,154,155). It is also reported that

α3 and α6 are also present in the brain [156,157]. Post-mortem brain sample studies showed the alteration of α4 & α7 nAchR in AD patients [158,159,160].

Angiotensin receptor

Angiotensin (AT) receptors, mainly AT1 receptor [161], play a vital role in peripheral activity and brain processes. Studies demonstrate that Angiotensin II receptor blockers (ARBs) are directly involved in neuroprotection in different part of brain like astrocyte, neurons, microglia and cerebrovascular endothelial cells [162]. ARBs are involved in many functions like anti-inflammatory compounds, inflammation triggered by glutamate excitotoxicity [163] and they also help in hippocampal synaptic signaling [164,165].

Non-amyloid-beta component precursor (NACP)

NACP is the type of presynaptic protein which is involved in amyloidogenesis and plaque formation [166,167,168,169,170]. NAC consists of long precursor (NACP) which produces NACP140 and NACP 112. [171,172]. Recent studies showed that NACP is a presynaptic nerve terminal protein [173,174,175] involved in neural plasticity, learning, and degeneration under the pathological condition in the AD.

c-Jun N-terminal kinases (JNK)

JNK which is also known as stress-activated protein kinase is triggered by exterior noxious stimuli via a kinase cascade [176; 177]. Activation of JNK phosphorylates serine-63 and 73 residues of C-jun and

enhances transcription activity of AP-1 complex [178,179]. Studies suggested that JNK-3 has role in neuronal apoptosis, neural tube defects and oxidative stress in AD patient [180,181,182,183].

DJ-1/PARK7

DJ-1 is mostly expressed in mammals and forms a homodimer associated with neurodegenerative diseases. Some factors are involved in disruption of DJ-1 structure like monogenic mutants and chemical modification of cysteine residues. PARK7 gene is responsible for encoding of DJ-1 which has many functions like an antioxidant, molecular chaperon, protein degeneration and transcriptional regulation. DJ-1 has been reported for suppression of neurodegenerative diseases in the animal model. DJ-1 could be used as a therapeutic target for the AD [184].

Triggering receptor expressed on myeloid cells 2 (TREM2)

In the previous years, genetic studies have helped in the identification of variants in immune-related genes involved in the progression of AD [185]. Studies suggested that TREM2 have high-risk factors for developing of the AD. [186,187]. TREM2 is expressed on myeloid cells 2 (TREM2) which belong to immunoglobulin superfamily. Expression of TREM2 in the AD brain is primarily overexpressed on plaque-associated myeloid cells like Microglia, peripheral monocytes and brain-resident macrophages [188,189,190,191,192]. These cells are responsible for causing AD pathogenesis. Studies reported that TREM2 deficiency helps in reducing accumulation of myeloid cells around plaques and amyloid pathology in AD mouse model. [193,194,195].

Table 1. Source and functions of all Alzheimer's disease therapeutic targets

S.No.	Name of target	Source	Functions	References
1.	β-Secretase	Astrocyte	Formation of Aβ	[9,10,11]
2.	Butyrylcholinesterase	Basal forebrain	Neuritic plaques and neurofibrillary tangles	[19,20]
3.	γ-Secretase: Presenilin I	Medial temporal lobe cortex	Formation of Aβ	[196]
4.	CP-AMPARs	Hippocampi	Boost synaptic Ca2+	[23]
5.	Calcitonin gene- regulated peptide	Hypothalamus, ventromedial nucleus of the thalamus, amygdala, grey matter, hippocampus and denate gyrates	Neurotransmitter	[197]
6.	Phosphodisterase (PDE)	Hippocampus, Cortex stratium	Hydrolysis of CGMP	[38,39,40,41,42,43,44]
7.	Muscarinic acetylcholine receptor (mAchR)	Hippocampus	Hyperphosphorylation of tau protein	[56,58]
8.	Dopamine 2 receptor	Central nervous system	Aβ plaques	[68,70]
9.	Gama aminobutyric Acid A receptor	Cerebral cortex, temporal lobes, frontal and occipital lobes	Neurotransmitter in cerebral cortex	[71, 73,74,75,198]
10.	Nuclear facto r E2 related factor-2 (Nrf2)	Temporal lobe, microglia and astrocytes	Antioxidant Maintaining redox balance and eliminate damage proteins	[80,81]
11.	Gamma-secretase metabotropic glutamate receptor	Cortical and Hippocampal	Releasing of ca2+	[91]
12.	Parkinson disease protein 7(DJ-1/PARK7)	Hippocampus	Antioxidant, molecular chaperon, protein degeneration and transcriptional regulation	[184]
13.	N-myc downstream-regulated gene 2	Astrocytes, glia cells	Differentiation, cell proliferation and cell apoptosis	[199]
14.	Serotonin 5-HT6 receptor	Cortical	Improving cognition dysfunction, synaptic plasticity	[100,101]
15.	Protein tyrosine phosphatase 1B (PTP1B)	Hippocampal, microglial	Learning, memory, endoplasmic reticulum, stress, regulation of synapse dynamics and microglial mediated Neuroinflammation.	[108]
16.	Monoamine oxidase B (MAO-B)	Astrogila, hippocampus, cerebral cortex and astrocyte	Metabolism of monoamine neurotransmitter	[111,112]
17.	NAD (P)H Quinone oxidoreductase 1		Oxidative stress, abnormality in redox balance	[113,114]
18.	Neurotrophic Receptor Tyrosine Kinase 1	Basal forebrain Nucleus Basalis (NB)	Development of CNS and PNS, promotion of cell survival	[53,118,119,120, 121, 122,123]
19.	Amyloid protein precursor (APP)	Hippocampus, olfactory bulb	Formation of Aβ	[200]
20.	Peroxisome proliferator activated receptor-γ	Astrocytes and microglial cells	Lipid storage, adipocyte differentiation, and lipid storage and glucose homeostasis	[132]
21.	C-C chemokine receptor type-5	Cortical neurons, hippocampal	Recruitment of leukocytes to inflammatory sites	[144,145, 146,147,148, 149,150]
22.	Nicotinergic acetylcholine receptor	Cerebral cortex	Cognitive, memory function and also involve in progression of sensory information	[151,152]
23.	Angiotensin receptor	Astrocyte, neurons, microlia and cerebrovascular endothelial cells	Anti-inflammatory compounds synaptic signalling	[164,165]
24.	Non-amyloid-beta component precursor	Neocortex, hippocampus, olfactory bulb, Striatum, thalamus, and cerebellum	Amyloidogenesis and plaque formation	[166,167,168,169,170]
25.	c-Jun N-terminal kinases	Cortex hippocampus and cerebellum	Neuronal apoptosis, neural tube defects and oxidative stress	[201]
26.	Triggering receptor expressed on myeloid cells 2	Myeloid cells	amyloid pathology	[188,189,190]

Table 2: List of approved Alzheimer's drugs and their targets

S.No.	Approved drug	Target	References
27.	Donepezil	Acetylcholinesterase	[202,203, 204]
28.	Rivastigmine	Acetylcholinesterase	
29.	Galantamine	Acetylcholinesterase	
30.	Memantine	NMDA receptor	[205]

Conclusion

Dementia is increasing rapidly in world population. Alzheimer's disease is an important factor behind development of dementia in older people. Due to the unclearly known mechanism of pathophysiology and target identification Alzheimer's disease treatment remains as a great challenge for modern drug discovery. Only few targets and drugs are available for the treatment of the disease. In this review, we have focused on several known targets which are directly and indirectly involved in generation of amyloid beta and neurofibrillary tangle in AD as well as other molecules. These targets are found in different regions of the brain like Hippocampus, astrocyte, glial cells, temporal, frontal lobe, cortex, Striatum, thalamus, cerebellum and Basal forebrain Nucleus Basalis (NB). These parts of the brain have different types of functions like synaptic plasticity, Long-term potentiation, memory formation, oxidative stress, Neuronal apoptosis, Anti-inflammatory, cell survival etc. Finally the molecules that are involved in unbalancing normal functioning of these functions have been highlighted in this review. There is urgent need to explore these targets for designing efficient Alzheimer's drugs with minimum side effects.

Abbreviations

FAD: Familial Alzheimer's disease; SAD: Sporadic Alzheimer's disease; EOAD: Early Onset Alzheimer's disease; LOAD: Late-onset Alzheimer's disease; APOE: Apolipoprotein E; APP: Amyloid Precursor Protein; BACE: Beta-secretase; NFT: Neurofibrillary tangle; PSEN: Presenilin; BuchE: Butyrylcholinesterase; CP-AMPARs: Calcium-permeable AMPA receptors; AchE: Acetylcholinesterase; CGRP: Calcitonin gene-related peptide; CAMP: Cyclic adenosine monophosphate; CGMP: Cyclic guanosine monophosphate; PDE: Phosphodiesterase; mAChR: Muscarinic acetylcholine receptor; MAO-B: Monoamine oxidase B; NDRG2: N-myc downstream-regulated gene 2; PTP1B: Protein tyrosine phosphatase 1B; NADPHQ1: NAD (P)H Quinone oxidoreductase 1; NRTK1: Neurotrophic receptor tyrosine kinase 1; PPAR-γ: Peroxisome proliferator activated receptor-γ; nAchR: Nicotinergic acetylcholine receptor; TREM2: Triggering receptor expressed on myeloid cells 2; JNK: c-Jun N-terminal kinases; PARK7: Parkinson disease protein 7; ARBs: Angiotensin II receptor blockers; TMs: Transmembrane-segment.

Acknowledgements

Author Contributions

AC and AM surveyed literature and prepared the manuscript. SS, BSY and PKM helped in writing the manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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