Novel Therapeutic Targets for Treating Alzheimer's Disease

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Abstract Alzheimer's disease is a progressive neurodegenerative disorder which is characterized by Amyloid β (Aβ) plaques and neurofibrillary tangles (NFTs). These characterized features cause mitochondrial dysfunction, oxidative stress, synaptic dysfunction, cognitive deficits, neuroinflammation, and ultimately lead to neurodegeneration. Although the current AD treatments are successful, they are limited due to their only symptomatic treatment. In the past few decades, much research has been focussing on targeting Aβ and NFTs which are hypothesized to prevent neurodegeneration. These strategies failed clinically, thus shifting the focus onto newer targets. In the present book chapter, we will emphasis on the current therapeutic targets, focussing on mitochondrial dysfunction, synaptic dysfunction, and neuroinflammation.

Keywords Alzheimer's disease · Neurofibrillary tangles · Amyloid β (Aβ) plaques · Mitochondrial dysfunction · Neurodegeneration

Abbreviations

Ach	Acetylcholine
AD	Alzheimer's disease
APP	Amyloid precursor protein

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Aβ	Amyloid β
BuChE	Butyrylcholinesterase
CREB	Cyclic AMP response element-binding protein
D2	Dopamine (D2) receptor
GABA	Gamma-aminobutyric acid
HD	Huntington's disease
IMM	Inner mitochondrial membrane
LTP	Long-term potentiation
MAO-B	Monoamine oxidase B
MS	Multiple sclerosis
mtDNA	Mitochondria contain their own DNA
NAD	Nicotinamide adenine dinucleotide
NFT	Neurofibrillary tangles
NMDA	*N*-methyl-D-aspartate
PD	Parkinson's disease
PDE	Phosphodiesterase
PGC-1α	Peroxisome proliferator-activated receptor γ coactivator-1α
PPARα	Peroxisome proliferator-activated receptor alpha
PS1	Presenilin-1
RCC	Respiratory chain complexes
ROS	Reactive oxygen species
SP	Senile plaques
VPA	Valproic acid

1 Introduction

One of the most prevalent neurodegenerative diseases, Alzheimer's disease (AD), is primarily characterized by amyloid (Aβ) plaques and neurofibrillary tangles (NFTs), which lead to dementia. Globally, about 47 million people live with dementia. By 2050, it is anticipated that this figure would surpass 131 million (Chaudhary et al. 2018). The "amyloid cascade hypothesis" states that the amyloid precursor protein (APP) is processed by aβ and γ-secretase to produce Aβ40 and Aβ42 peptides, which go on to form oligomers and aggregates and deposit Aβ plaques. Additionally, tau protein hyperphosphorylation results in NFT production. The hallmarks of AD, including synaptic failure, vascular damage, increased oxidative stress, neuronal and axonal injury, microglia-regulated neuroinflammation, and mitochondrial dysfunction, are facilitated by intraneuronal NFTs and extra-neuronal senile plaques (SP) comprised of Aβ peptides.

To date, cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and *N*-methyl-D-aspartate (NMDA) receptor inhibitors (memantine) have been used to treat AD. None of these medications are curative or disease-modifying; instead, they merely temporarily or symptomatically relieve some AD patients. There is a

continuous quest for innovative therapeutic targets because these medications are only marginally effective, unable to stop cognitive deterioration, and also have numerous undesirable side effects.

The key pathological hallmarks of AD, extracellular Aβ deposition, and the emergence of intracellular NFTs have been the subject of growing investigation in recent years. Aβ-peptides were once thought to be one of the most promising AD treatment candidates. Unfortunately, despite promising clinical results so far, many clinical investigations based on the Aβ cascade theory were unsuccessful (Doody et al. 2014, p. 3; Salloway et al. 2014). Clinical trials targeting NFTs, which are known to impede axonal transport and cause synaptic dysfunction, have not been able to enhance cognition (Mohandas et al. n.d.; Pedersen and Sigurdsson 2015). The clinical failure of numerous Aβ- and NFT-based treatments gave rise to the idea that AD is a multifactorial illness. While other treatment targets still need to be researched, these regions nonetheless promise the development of AD therapeutics (Calvo-Flores Guzmán et al. 2018).

Currently, many targets including beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), Gamma Secretase, Butyrylcholinesterase (BuChE), Phosphodiesterase (PDE), Gamma-aminobutyric acid (GABA), Dopamine (D2) receptor, Nrf2, Acetylcholine (Ach) receptor, Amyloid precursor protein (APP), and Monoamine oxidase B (MAO-B) are being considered for anti-Alzheimer's drug discovery (Chaudhary et al. 2018). 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 correspond to various functions like synaptic plasticity, long-term potentiation (LTP), memory formation, oxidative stress, neuronal apoptosis, anti-inflammatory, cell survival, etc. Some of these targets are already having known inhibitors, while others are still being investigated for designing suitable ligands against them.

Apart from these established targets, some novel therapeutic targets are emerging due to increasing need for the effective treatment of AD. Such targets include Purinergic receptor (P2X7R), PPAR-α, proteins associated with synaptic dysfunction, and mitochondrial dysfunction (Table 1). In this chapter, we focus on the above targets and their therapeutic efficacy in AD.

Table 1 Alzheimer's disease therapeutic targets

Established targets	Novel targets
• Beta-site amyloid precursor protein cleaving enzyme 1 (BACE1)	• Purinergic receptor (P2X7R)
• Butyrylcholinesterase (BuChE)	• Proteins associated with synaptic dysfunction
• Phosphodiesterase (PDE)	• Proteins and enzymes associated with mitochondrial dysfunction
• Gamma-aminobutyric acid (GABA)	• Peroxisome proliferator-activated receptor alpha (PPAR-α)
• Dopamine (D2) receptor	
• Acetylcholine (Ach) receptor	
• Amyloid precursor protein (APP)	
• Monoamine oxidase B (MAO-B)	

2 Novel Therapeutic Targets for Alzheimer's Disease

2.1 Purinergic Receptor (P2X7R)

Purinergic receptors are well known for their therapeutic role in different diseases, including Multiple Sclerosis (MS), AD, Huntington's disease (HD), cancer, rheumatoid arthritis, ischemia and inflammatory pain, and Parkinson's disease (PD). P2X7 receptor (P2X7R) belongs to the class of Purinergic receptors (P2), which is highly expressed in immune cells, particularly in those engaged in the innate immune response such as macrophages, monocytes, and specifically microglia (Di Virgilio et al. 2018; Wei et al. 2018).

P2X7R structure includes large extracellular domain (282 amino acids), short intracellular N-terminal domain (26 amino acids), an intracellular C-terminal domain (239 amino acids), and 2 short transmembrane domains (24 amino acids each) constituting a total of 595 amino acids (Jiang et al. 2013). Intracellular domain is important in regulation of Ca^{2+} influx and activation of ERK ½ pathway contributing to the permeation of channel. When compared to other subtypes of P2X receptor, P2X7R contains a large C-terminal domain which consists of many motifs and sub-domains related to multiple functions. These sub-domains include LPS-binding motif, Src homology 3 binding domain, death domain, and binding sites for various cytoskeletal proteins (Chen et al. 2021).

Highest density of P2X7Rs is located at CNS microglia. ATP is the physiological agonist for P2X7R. Extracellular aggregation of Aβ peptides triggers glial cell activation and the release of ATP, therefore stimulating purinergic receptors, especially P2X7R (Illes et al. 2019). In support of this, upregulation of P2X7R has been found near Aβ plaques and microglia (Parvathenani et al. 2003; McLarnon et al. 2006). Also, it is reported that activation of P2X7R enhances the migration of senile plaques through microglia (Martínez-Frailes et al. 2019). Activation of P2X7R converts the resting microglia to activated microglia, in which the latter generates pro-inflammatory cytokines including IL-1β, IL-6, IL-18, TNF-α, several types of reactive oxygen species (ROS), and chemokines such as CCL2 and CCL3 (Shieh et al. 2014; He et al. 2017).

The surface of microglia is expressed with collection of pattern recognition receptors (toll like receptors-TLRs) that stereotypically detect pathogen-associated molecules (such as lipopolysaccharide; LPS) or danger-associated molecular patterns (DAMPS) (such as ATP). There are two signals involved in the production of IL-1β. One is through TLRs which recognize DAMPs, Aβ, LPS, etc. and activate NFkB pathway, thus translation of pro-IL-1β to IL-1β. P2X7R activation is the other signal. However, activation of this receptor induces assembly and activation of NLRP3 inflammasome (which is composed of NLRP3-nucleotide binding, leucine-rich repeat, pyrin domain containing 3, ASC-apoptosis-associated speck-like protein-containing caspase recruiting domain, and pro-caspase-1). Then, NLRP3 inflammasome converts pro-caspase-1 to caspase-1, which thereby cleaves the biologically inactive pro-interleukin-1β to interleukin-1β (IL-1β) (Fig. 1)

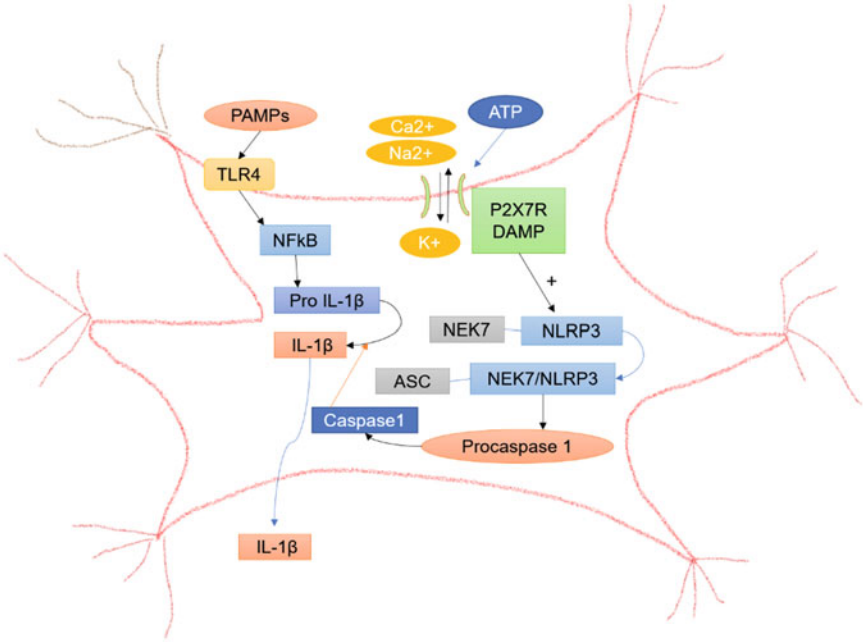

Fig. 1 P2X7R in microglia [generation of interleukin-1β (IL-1β)]: pathogen-associated molecular protein (PAMPs), danger-associated molecular protein (DAMPs), Toll-like receptor 4 (TLR4), NIMA-related kinases (NEK7), nucleotide-binding leucine-rich repeat pyrin domain containing 3 (NLRP3), and apoptosis-associated speck-like protein (ASC)

(Muñoz-Planillo et al. 2013). Upon LPS priming, P2X7Rs also enhance inflammatory cytokine response sequentially by IL-1β, IL-6, and tumour necrosis factor-α (TNF-α) (Young and Górecki 2018; Bhattacharya and Jones 2018). The critical role of P2X7Rs in the secretion of IL-1β makes it an attractive therapeutic target.

It is reported that IL-1β is involved in the formation of Aβ plaques, hyperphosphorylation of tau, and synaptic plasticity impairment (Smith et al. 2012). Besides this activation of NLRP3, inflammasome promotes deposition of tau protein in a mouse model of Frontotemporal dementia (FTD) (Lemprière 2020). Some studies confirmed that P2X7R upregulation in activated microglia was parallel with AD progression by using two different mouse models of AD (APP/PS1 mice and J20 mice) (Lee et al. 2011; Martínez-Frailes et al. 2019). A recent study reported that PS2-deficient mice are most sensitive to Aβ-induced neuroinflammation due to the upregulation of P2X7R in both glial and neuronal cells in a transcription factor Sp1 (SP1)-dependent manner (Qin et al. 2017). Different studies using both in vitro and in vivo approaches postulated that P2X7R might be one of the factors controlling APP processing (Delarasse et al. 2011; León-Otegui et al. 2011; Diaz-Hernandez et al. 2012; Darmellah et al. 2012). Furthermore, role for P2X7R in the phagocytosis of Aβ peptides was also reported to contribute to Aβ clearance. Another study reported that P2X7R might also down-regulate pathological microglial activation in AD (Martin et al. 2019).

Further, pharmacological blockade or knocking out the P2X7R in different AD mouse models has shown neuroprotective effects by reducing neuroinflammation (Ryu and McLarnon 2008; Chen et al. 2018; Martin et al. 2019). Initial studies demonstrated that in vivo pharmacological inhibition of P2X7R by Brilliant Blue G (BBG) attenuated inflammatory response and diminished leakiness of BBB in $A\beta_{1-42}$-induced AD model (Ryu and McLarnon 2008). In accordance, later study revealed that in vivo inhibition of P2X7R by BBG prevented the spatial memory impairment and cognitive deficits in AD mouse model (Chen et al. 2014). The reversal of the $A\beta_{1-42}$-induced morphological and cognitive effects by BBG proved the involvement of P2X7Rs. In another study, administration of oxidized ATP (o-ATP), a P2X7R antagonist, attenuated microglial activation and neuronal damage in LPS-induced AD model (Choi et al. 2007). Moreover, APP/PS1/P2X7R-deficient mice exhibited smaller cognitive deficit and better synaptic plasticity than APP/PS1 mice (Martin et al. 2019). Another study demonstrated that P2X7R plays a critical role in Aβ peptide-mediated release of chemokines, particularly CCL3, which is associated with pathogenic $CD8^+$ T cell recruitment. This study highlights a novel detrimental function of P2X7R in chemokine release and supports the notion that P2X7R may be a promising therapeutic target for AD (Martin et al. 2019).

Another pathological feature of AD is impaired phagocytosis ability. A genome-wide association study revealed various genes associated with phagocytosis function of microglia such as TREM2 and CD33 (Efthymiou and Goate 2017). Further, it is reported that reduced phagocytic capacity results in increased amyloid deposition in AD mouse model (Parhizkar et al. 2019). It is believed that P2X7R shows scavenger activity. A study reported that high level of P2X7R mediates phagocytosis of apoptotic lymphocytes in HEK-293 cells were tranfected with P2X7R and macrophages to acquire the ability to phagocytose apoptoticlymphocytes (Gu et al. 2011). This study explains that involvement of P2X7R in its un-activated state acts as scavenger receptor. Further, experiments on microglia have shown that P2X7R activation attenuated their phagocytic capacity (Janks et al. 2018; Martínez-Frailes et al. 2019).

ROS is another effector of microglia by P2X7R activation. Several pieces of evidence point to the fact that P2X7R may be the primary receptor involved in the generation of ROS (Ex: H_2O_2) by activating microglial cells (Nuttle and Dubyak 1994). In vitro studies revealed that fibrillar $A\beta_{1-42}$ causes ROS production generated via P2X7R activation induced by ATP released from rat microglial cells in an autocrine manner (Kim et al. 2007; Liu et al. 2020). Hence, P2X7R upregulation in microglial cells may result in excessive ROS production induced by Aβ which contributes to the synaptic toxicity associated with the early stages of AD (Lee et al. 2011). In vivo administration of selective P2X7R antagonist A438073 avoided ROS production and oxidative DNA damage induced by P2X7R activation in spinal cord dorsal horn neurons (Munoz et al. 2017). Furthermore, P2X7Rs drive proliferation and activation of microglia, upregulating their surface expression of immunomodulatory proteins and becoming efficient in producing a variety of cytokines, chemokines, and ROS (Monif et al. 2009, 2010). All these studies suggest that BBB permeable compounds and selective P2X7R antagonists might be considered as

good therapeutic drugs to treat chronic neuroinflammation associated with AD. Therefore, P2X7R antagonists may become general anti-neuroinflammation and anti-neurodegeneration remedies, also improving late-onset AD.

2.2 Proteins Associated with Synaptic Dysfunction

Synaptic plasticity events are crucial for synaptic functions including learning and memory processes, where short-term alterations in synaptic strength are converted to long-lasting memories. Apart from the presynaptic terminal and the postsynaptic compartment, synapse also includes astrocytes and the extracellular matrix creating a tetrapartite synapse. Synaptic transmission strength is based on changes in neuronal activity where long-term potentiation (LTP) and long-term depression (LTD) represent the functions of learning and memory. Synaptic transmission majorly relies on multiple cellular mechanisms which include biosynthesis of neurotransmitters (NTs) from amino acids and delivery of synthesized NTs to synaptic sites. This requires proper formation of synaptic vesicles, intact microtubule tracts, and timely removal of NTs from synaptic cleft after neurotransmission (Pelucchi et al. 2022).

N-methyl-D-aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methyl-4-364 isoxa-zolepropionic acid (AMPA) receptors together regulate excitatory synaptic transmission and plasticity in brain, thus playing critical role in learning and memory. Altered internalization of AMPA receptors affects synaptic plasticity inducing synaptic dysfunction and loss of dendritic spines. Aβ-induced excitotoxicity in postsynaptic neurons associated with more Ca^{2+} influx leads to increased ROS production, tau hyperphosphorylation, and lipid peroxidation, altogether contributing to synaptic dysfunction. Moreover, Aβ-induced tau hyperphosphorylation destabilizes microtubules which alter axonal trafficking of mitochondria and translocation of tau to dendritic spines. This further contributes to NMDA receptor destabilization and excitotoxicity and has a detrimental effect on synaptic function (Tönnies and Trushina 2017).

Synaptic dysfunction is one of the common pathogenic traits in many neurological disorders. In AD, the degeneration of synapses can be detected at the early pathological progressions before achieving complete neuronal degeneration, supporting the hypothesis that synaptic failure is a major determinant of AD. Most of the Aβ plaques generate and form oligomers at the synaptic region. All the elements constituting the tetrapartite synapse are altered in AD and can synergistically contribute to synaptic dysfunction (Marsh and Alifragis 2018). Moreover, the two main hallmarks of AD, i.e. Aβ and NFT's, collectively cause synaptic deficits. Deciphering the mechanisms underlying synaptic dysfunction is relevant for the development of the next-generation therapeutic strategies, aimed at modifying the progression of AD.

The targets of Aβ at synapse have been identified as dendritic or axonal compartments (overexpression of APP) and plasticity in nearby neurons, ultimately leading to reduction in spine density (Marcello et al. 2012). It has been hypothesized that Aβ

peptides enhance neurotransmitter (NT) release. Several reports suggested that key proteins which regulate the interaction of synaptic vesicles (SVs) with the presynaptic membrane or the availability of SVs to participate in NT release are affected by Aβ peptides (Yang et al. 2015; Russell et al. 2012). Proteins involved in SV docking and fusion that regulate NT release are Syntaxin 1a (Stx1a), Synaptophysin (Syp1), dynamin, and Synapsin1 (Snp1) (Kelly et al. 2005; Liu et al. 2019) (Fig. 2).

The prolonged phosphorylation of Snp1 would enhance neurotransmission by increasing the availability of SVs that would dock to the active zone. Furthermore, disruption of the Syp1/VAMP2 complex (VAMP2 known as Synaptobrevin 2) on these vesicles would increase the accessibility of VAMP2 to the other SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) proteins, promoting the SNARE complexes formation and enhancing the probability of NT release (Marsh and Alifragis 2018) (Fig. 2). Moreover, an Aβ-mediated increase of Ca^{2+} levels inside the pre-synapse would also enhance SV fusion and the release of glutamate. This aberrant release of glutamate would initially activate NMDARs, but eventually induce excitotoxicity. In the long term, the extensive use of SVs combined with endocytic defects and recovery due to the inactivation of dynamin and sustained phosphorylation of Snp1 would gradually deplete these vesicles from the synapse, thereby reducing synaptic activity. However, depletion of SV reserve pools after prolonged exposure to Aβ in neuronal cultures has been reported (Parodi et al. 2010; Kelly et al. 2005). Further, Park et al. showed that exposure of neurons to Aβ reduces the activity-dependent lateral dispersion of SVs, providing significant evidence that Aβ reduces SV mobility (Park et al. 2017).

The sustained phosphorylation of Snp1 might be the underlying cause for the inhibition of inter-synaptic vesicular movements, thereby disrupting the Syp1/VAMP2 complex by Aβ which could be one of the contributing factors for this inhibition. Collectively, these effects would have a substantial impact on the gradual progression of synaptic dysfunction and ultimately cause synaptic deficit, which is a key hallmark of AD pathology.

Another major hallmark in AD is tau which is involved in synaptic dysfunction. Pathological modifications of tau protein alter its binding affinity and lead to aberrant aggregation and migration to different brain regions, which eventually lead to tauopathy in AD (Chen et al. 2019). Hyperphosphorylation of tau leads to its detachment with microtubules and further impairs axonal transport. Some studies revealed that uptake of extracellular localized tau by neurons triggered tau accumulation in axons and dysregulated the axonal transport of membrane organelles (Swanson et al. 2017; Wu et al. 2013). Some studies reported that abnormal tau binds to synaptic vesicles by synaptogyrin-3, thus disrupting presynaptic functions (McInnes et al. 2018; Zhou et al. 2017). Further, it is observed that accumulation of tau in presynaptic vesicles induces significant increase in NT release by intracellular calcium release, leading to synaptic depression (Moreno et al. 2016). Further, tau infiltration in dendrites results in reduced clustering of AMPA and NMDA receptors, which leads to compromised synaptic transmission and memory deficits (Hoover et al. 2010).

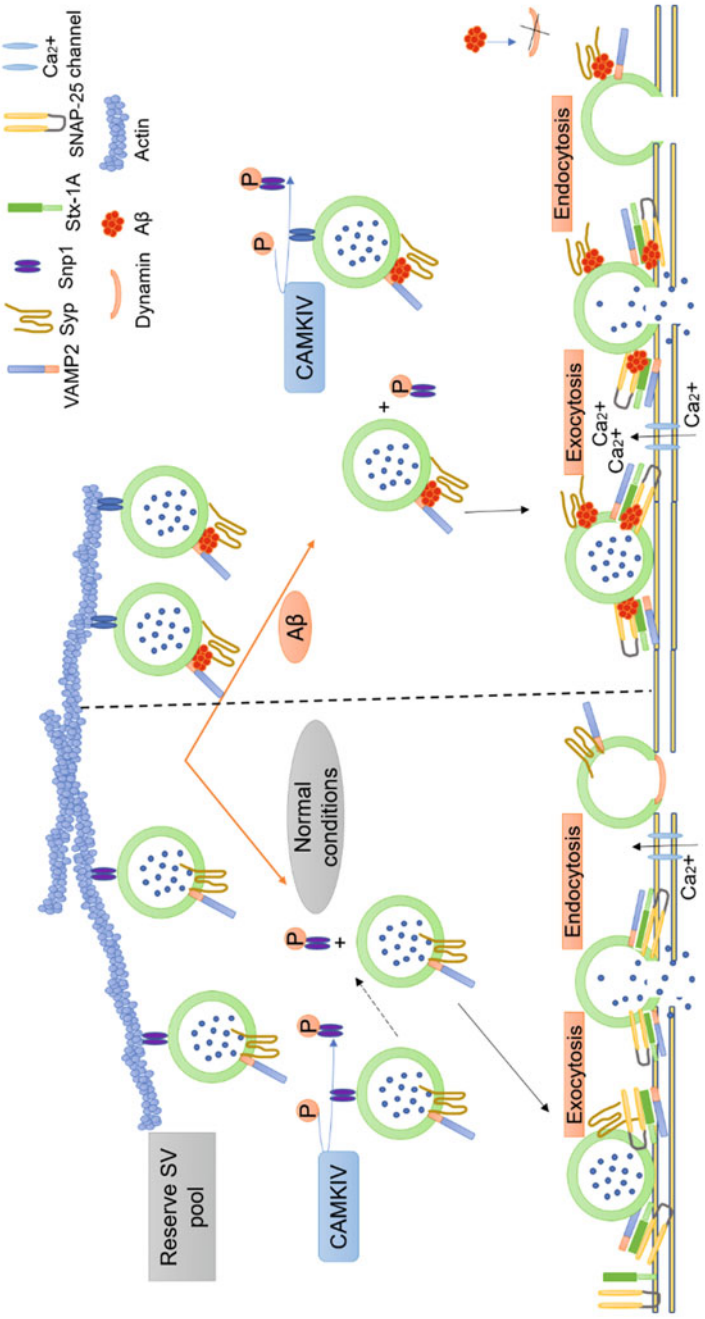

Fig. 2 Synaptic dysfunction associated with Amyloid β in Alzheimer's disease: (1) Under normal physiological conditions, release of neurotransmitter (NT) from synaptic vesicles (SVs) is tightly regulated by Snp1, Syp1/VAMP2 complex, Stx-1A, and dynamin1. (2) In the presence of Aβ, release of NT from SVs will be disrupted by Aβ by binding to Syp1/VAMP2 complex, thus leading to uncontrollable involvement of SVs in aberrant NT release. Further, this also leads to dysregulation of endocytosis by reducing the levels of dynamin1. This will eventually lead to disruption of SV pools

It is well established that primary kinase involved in the tau phosphorylation includes glycogen synthase kinase (GSK-3) and cyclin-dependent protein kinase 5 (Cdk-5). Multiple studies demonstrated the benefits of inhibiting GSK-3 which majorly includes reversing synaptic dysfunction. A study demonstrated that selective GSK-3 inhibitor AR-A014418 prevented LTP impairment and tau hyperphosphorylation induced by Aβ in wild-type mice (Shipton et al. 2011). Another study reported that GSK-3 inhibitors (lithium and kenpaullone) rescued LTP by upregulating mTOR pathway in AD mice model (Ma et al. 2010). Later, a study revealed that specific GSK-3 inhibitor CT-99021 has prevented Aβ-induced LTP in hippocampal cultures (Jo et al. 2011). Besides GSK-3, inhibition of Cdk-5 with roscovitine or butyrolactone prevented the Aβ-mediated block of LTP induction (Wang et al. 2004). All the above studies suggest that abnormal tau phosphorylation is an important factor in synaptic dysfunction.

Valproic acid (VPA) has been recognized which could be used to abrogate some of the early presynaptic defects (Marsh et al. 2017). VPA is a short-branched chain fatty acid, most commonly used to treat epilepsy and bipolar disorder. Studies on pre-clinical models suggest that VPA plays key roles such as affecting long-term potentiation (LTP) which could be therapeutic potential to combat AD (Zhang et al. 2003; Leng et al. 2008; Qing et al. 2008). Moreover, it has also been shown that it prevents Aβ-induced reduction in SV recycling and that it can induce clustering of Snp1 in developing neurons (Williams and Bate 2016; Hall et al. 2002). Although many evidences highlight the significance of Aβ peptides and tau hyperphosphorylation in the deregulation of NT release and dysfunction of SV dynamics, this area as new therapeutic target has been largely overlooked. Targeting these defects of synaptic function could serve as a target for crucial early intervention and diagnosis of AD.

2.3 Targeting Mitochondrial Dysfunction

Mitochondria are defined as the powerhouse of the cell because every cell in the human body relies on the energy provided by these organelles to sustain its vital functions. Mitochondrial energy production (process of oxidative phosphorylation) takes place at the inner mitochondrial membrane (IMM) through the activity of respiratory chain complexes (RCC), generating an inner membrane potential (mtΔΨ) that is used by the ATP-synthase enzyme complex to synthesize ATP (Cenini and Voos 2019). This process depends on the supply of reducing equivalents by the end-oxidation of nutrients via the Krebs cycle or β-oxidation in the mitochondrial matrix compartment (Stock et al. 2000). Mitochondria contain their own DNA (mtDNA) located in the matrix that encodes mainly 13 protein subunits of the RCC. Hence, the maintenance of an entire and functional mitochondrial proteome requires a fine-tuned and well-coordinated sequence of many reactions and a close integration of organellar and cellular biogenesis processes (Pfanner et al. 2019). A master regulator of mitochondrial biogenesis is Peroxisome proliferator-activated

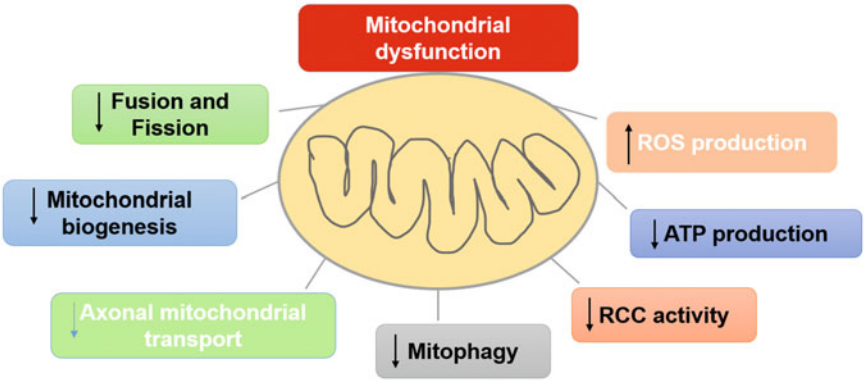

Fig. 3 Mitochondrial dysfunction and its associated pathologies

receptor γ coactivator-1α (PGC-1α) that activates a series of transcriptional factors (Scarpulla 2011).

The enzymatic activity of the mitochondrial RCC results in a leakage of electrons from the RCC, contributing significantly to the formation of ROS (Shariff et al. 2004) (Fig. 3). Therefore, ROS are considered a typical by-product of bioenergetic pathways (Quinlan et al. 2013). However, under normal physiological conditions, ROS production is well balanced by the presence of adequate antioxidant systems, and the damage to the diverse cellular constituents is contained. However, during ageing, as well as during several pathological conditions such as neurodegenerative diseases, this equilibrium becomes unbalanced. Increased ROS concentrations result in molecular damage at the site where they are produced or, through diffusion, in surrounding areas, leading to the generation of oxidative stress condition. The hippocampus region, cortex, and more generally the brain are particularly vulnerable to oxidative stress because of their high consumption of oxygen.

Neurons are strictly dependent on the presence of mitochondria, in particular at the synapses where these organelles produce ATP and buffer Ca^{2+} ion concentration, which are fundamental processes for the implementation of neurotransmission and generation of membrane potential along the axon (Li et al. 2004; Verstreken et al. 2005). This justifies the presence of high amount of mitochondria at the synaptic area, higher than any other part of the neurons. Linked to that, an efficient transport of neuronal mitochondria at the synaptic terminals is fundamental for their correct function.

Mitochondrial dysfunction is one of the factors that may actively contribute to AD onset and progression. In 2004, a new hypothesis called mitochondrial cascade hypothesis (apart from Amyloid cascade hypothesis) was proposed to explain the onset of sporadic AD, which explains that the mitochondrial dysfunction is the primary process to trigger a cascade of events that lead to sporadic late-onset AD (Swerdlow and Khan 2004) (Fig. 3).

The analysis of the samples from different AD experimental models and AD patients showed a strong link between the oxidative stress and mitochondrial

dysfunction. In the transgenic mice over-expressing human APP (Tg mAPP mice), an early and progressive accumulation of Aβ peptide in synaptic mitochondria led to a mitochondrial synaptic dysfunction such as damaged mitochondrial respiratory activity, oxidative stress, and impaired mitochondrial axonal transport (Du et al. 2010). In another study, it is reported that the compromised mitochondria bioenergetics together with elevated oxidative stress levels are early phenomena appearing before the development of observable Aβ plaques in 3xTg-AD mice (Hauptmann et al. 2009; Yao et al. 2009). The mitochondrial dynamics such as fusion and fission processes were found unbalanced in AD, potentially leading to compromised distribution and morphology of mitochondria in the neurons (Hirai et al. 2001) and fragmented mitochondria brains from AD patients (Wang et al. 2008a, 2009). Furthermore, the level of proteins regulating the mitochondrial biogenesis such as PGC-1α, NRF1 and 2, and TFAM was significantly reduced in hippocampus and cellular models overexpressing APP Swedish mutation (Qin et al. 2009; Sheng and Cai 2012). In the AD mouse model of mutant human transgenes of APP and Presenilin-1 (PS1), the mitochondrial biogenesis markers were found declined in the hippocampus region (Song et al. 2018).

The two major and typical histopathological markers of AD, Aβ peptide and tau, harmfully accumulate in mitochondria (Eckert et al. 2010). Aβ peptide and abnormal tau negatively affect axonal transport and consequently the transport of mitochondria along the axon from the neuronal soma to synapses. Several AD models such as transgenic models (APP overexpression) or Aβ-induced AD are characterized by mitochondrial fragmentation and abnormal mitochondrial distribution along the neurons due to alteration of mitochondrial fusion and fission proteins levels (Wang et al. 2008b; Zhao et al. 2010; Calkins and Reddy 2011). All these results lead to two critical remarks: (a) Altered balance between fusion and fission that interferes with mitochondrial transport contributes actively to AD pathogenesis and (b) Mitochondrial dynamics impairment could be a new therapeutic target in AD.

Mitochondria could be targeted through two ways: (a) by pharmacologic approaches acting on mitochondria directly or (b) by action on the lifestyle that indirectly hits this organelle. Pharmacological approaches include Antioxidants, Phenylpropanoids, Mitophagy stimulators, and some miscellaneous compounds such as Oxaloacetate, Nicotinamide adenine dinucleotide (NAD), Pioglitazone, Dimebon (Table 2). Second approach, i.e. Action on Life style, includes calorie restriction, diet, and exercises.

2.4 Peroxisome Proliferator-Activated Receptor Alpha (PPARα)

The first PPAR currently known as PPAR-α was discovered in 1990 (Issemann and Green 1990). PPAR-α regulates oxidative stress, energy homeostasis, andbmitochondrial fatty acids metabolism including fatty acids β oxidation pathway and is the only receptor belonging to PPAR family which influences excitatory

Table 2 Effect of pharmacological approaches on mitochondria in experimental models of AD

Pharmacological approach	Observed effects	AD model
Antioxidants		
Selenium	• Inhibition of ROS production and oxidative damage	• In vitro Aβ42-CFP-overexpressed HEK293 cell line (Chen et al. 2013)
	• Reduction of mitochondrial membrane depolarization	
Coenzyme Q10	• Attenuation of decreased oxidative phosphorylation efficiency and increased H_2O_2 production	• Isolated mitochondria from Aβ1-40 peptide-treated diabetic Goto–Kakizaki aged rats (Moreira et al. 2005)
	• Decreased levels of Aβ and improved cognitive performance	• In vivo Tg19959 mice (Dumont et al. 2011)
	• Reduction of mitochondrial accumulation of Aβ peptide	
Catalase	• Reduction of abnormal APP process, oligomeric Aβ peptides, and BACE1 activity and levels, and oxidative damage	• In vivo MCAT/APP mice (Mao et al. 2012)
	• Increase of protective soluble APPα and CTF83 fragments	
α-Lipoic acid	• Decrease of mitochondrial-related oxidative stress and apoptotic markers	• In vitro AD fibroblast (Moreira et al. 2007)
	• Preservation of COX assembly elevation of ATP levels, Krebs cycle dehydrogenase, complex I, and COX activities	• In vivo aged Wistar rats (Ajith et al. 2014)
Phenylpropanoids		
Resveratrol	• Attenuated Aβ induced cytotoxicity, apoptosis, and intracellular ROS accumulation	• In vitro Aβ peptide-treated PC12 cell line (Jang and Surh 2003)
	• Prevents memory loss	• In vivo APP/PS1 mice (Porquet et al. 2014)
Wogonin	• Rescue the mtΔΨ loss	• In vitro Tet-On Aβ42-GFP-overexpressed SH-SY5Y cell line and
	• Attenuation of mitochondria-mediated apoptosis	• In vivo 3xTg-AD mice (Huang et al. 2017a)
Epigallocatechin-3gallate (EGCG)	• Restored mitochondrial respiratory rates, MMP, ROS production, and ATP levels	• Neuroblastoma cells expressing mutant APP and APP/PS-1 transgenic mice (Dragicevic et al. 2011)

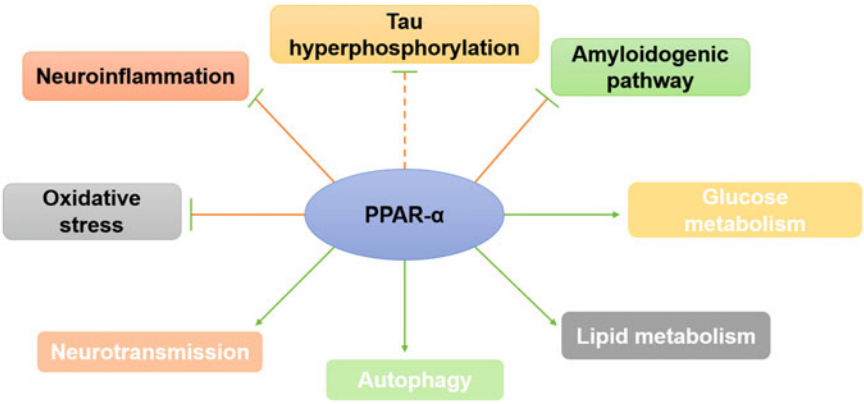

Fig. 4 PPAR-α and its associated pathologies in Alzheimer's disease

glutamatergic neurotransmission and also cholinergic/dopaminergic signaling in the brain. Additionally, PPAR-α is engaged in metabolism of APP in the brain, and directly or indirectly through Aβ, it may also influence tau protein phosphorylation (Fig. 4) (Wójtowicz et al. 2020). PPAR-γ, PPAR-α, and their coactivator PGC-1α play an important role in cell differentiation and mitochondria biogenesis in neurodegeneration and neuroinflammation (Austin and St-Pierre 2012; Scarpulla 2011).

Roy et al. determined the distribution of PPAR-α in different regions of hippocampus and observed that PPAR-α protein was localized in CA1, CA2, and CA3 and in dentate gyrus (DG) of mice brain (Roy et al. 2013). It was found that PPAR-α controls calcium influx and the expression of several genes encoding hippocampal proteins involved in the regulation of synaptic plasticity. PPAR-α is also engaged in expression of NMDA receptor subunit NR2A and NR2B genes, AMPA receptor [2-amino-3(3-hydroxy-5-methyl-isoxasol-4-yl) propanoic acid] associated subunit GluR1, and also AMPA-receptor associated activity-related cytoskeleton proteins (Sakimura et al. 1995; Lee et al. 2003; Tzingounis and Nicoll 2006). All these mentioned genes are related to synaptic plasticity and are regulated by PPAR-α via cyclic AMP response element-binding protein (CREB). Further, many studies demonstrated that PPAR-α and its ligands are involved in regulation of glutamatergic and cholinergic-mediated dopaminergic transmission in the brain (Huang et al. 2017b; Zakrocka et al. 2017; Melis et al. 2010, 2013). However, further studies are necessary to understand the role of PPAR-α in glutamatergic and other signaling pathways in physiological conditions and in AD. The above functions indicate that PPAR-α could be promising target for therapy of AD. Further, the mechanism of its action in the brain should be characterized in depth to enable successful application.

Activation of PPAR-α receptor with specific receptor agonist enhanced transcription of GluA1 subunits of the AMPA receptor which further leads to an AMPA response and better synaptic plasticity (Schmitt et al. 2005). In another study, it is reported that under basal physiological conditions, PPAR-α is involved in the

degradation of APP by activation of β and α secretases leading to liberation of non-amyloidogenic peptide (p3) and soluble sAPPα with possible neuroprotective effect (Corbett et al. 2015). Further, Zhang et al. demonstrated that PPAR-α agonist (GW7647) regulates Aβ generation by inhibition of BACE-1 activity (Zhang et al. 2015). The above studies suggest that alteration of PPAR-α signaling may lead to activation of APP metabolism and Aβ liberation/accumulation through amyloidogenic pathway in AD.

The studies of Vallee and Lecarpentier on AD described that PPAR agonists diminish learning and memory deficit in AD patients (Vallée and Lecarpentier 2016). Anti-amyloidogenic action of PPAR-α agonists (fibrates) was observed in clinic in longitudinal treatment of patients (Blasko et al. 2008). PPAR-α receptor stimulation induces synthesis of allopregnanolone in astrocytes (this hormone thought to be involved in neuroprotective mechanism) (Raso et al. 2011). Therapeutic effects of PPAR-α on neuronal death and microvascular impairment were described by Moran and Ma (2015). Gemfibrozil is a PPAR-α agonist that was undergoing Phase II Clinical trial for AD which downregulates the BACE1 expression (Clinical trial identifier: NCT02045056) (NeurologyLive n.d.). The above evidences and clinical studies suggest the therapeutic potential of targeting PPAR-α.

3 Conclusion

Nowadays, AD has been considered a multifactorial disease due to its numerous pathological cascades and their unclear mechanisms. Due to these reasons, therapy of AD remains a difficult challenge for discovery of novel treatments. Till now, only few Food and drug administration (FDA)-approved treatments are available. Yet, they are only symptomatic treatments and there is a further need to identify and explore new therapeutic targets that focus on main pathological hallmarks of the disease. In this chapter, we have discussed about the novel targets in the therapy of AD. These targets majorly focus on neuroinflammation, synaptic dysfunction, mitochondrial dysfunction, Aβ plaques, and tau hyperphosphorylation which are the crucial pathological events in AD.

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