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Review

New Insights into Alzheimer's Disease: Novel Pathogenesis, Drug Target and Delivery

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Abstract: Alzheimer's disease (AD), the most common type of dementia, is characterized by senile plaques composed of amyloid β protein (Aβ) and neurofilament tangles derived from the hyperphosphorylation of tau protein. However, the developed medicines targeting Aβ and tau have not obtained ideal clinical efficacy, which raises a challenge to the hypothesis that AD is Aβ cascade-induced. A critical problem of AD pathogenesis is which endogenous factor induces Aβ aggregation and tau phosphorylation. Recently, age-associated endogenous formaldehyde has been suggested to be a direct trigger for Aβ- and tau-related pathology. Another key issue is whether or not AD drugs are successfully delivered to the damaged neurons. Both the blood–brain barrier (BBB) and extracellular space (ECS) are the barriers for drug delivery. Unexpectedly, Aβ-related SP deposition in ECS slows down or stops interstitial fluid drainage in AD, which is the direct reason for drug delivery failure. Here, we propose a new pathogenesis and perspectives on the direction of AD drug development and drug delivery: (1) aging-related formaldehyde is a direct trigger for Aβ assembly and tau hyperphosphorylation, and the new target for AD therapy is formaldehyde; (2) nano-packaging and physical therapy may be the promising strategy for increasing BBB permeability and accelerating interstitial fluid drainage.

Keywords: Alzheimer's disease; drug delivery; extracellular space; blood–brain barrier; formaldehyde; interstitial fluid

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1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease associated with progressive cognitive decline. AD is the major type of dementia in 60–70% of cases. By 2050, the number of new cases of dementia will be over 1 million per year worldwide [1]. Even though more than 600 billion dollars have been invested in drug developments for AD treatment, the outcomes are insufficient [2]. The failures of research and drug development for AD force us to reflect on two critical questions: (1) Which endogenous factor initiates AD occurrence? (2) Do AD drugs successfully reach the damaged neurons?

The hypothesized causes of AD include amyloid cascade, presenilin, tau hyperphosphorylation, cholinergic, calcium imbalance, oxidative stress, etc. Two main factors have been proposed as the critical triggers of AD: amyloid and tau [3]. These hypotheses suggest that eliminating amyloid and hyperphosphorylated tau could improve cognition in AD patients, while major drugs targeting amyloid and tau proteins could not improve cognitive functions in clinical trials. Recently, calcium imbalance and oxidative stress were found to play an important role in the development of AD [4,5].

In fact, whether the medicines arrived at the targeted neurons in the brains is determined by at least two key structures, the blood–brain barrier (BBB) and brain extracellular space (ECS) [2]. The BBB is a barrier formed by vascular endothelial cells and a variety of glial cells. The BBB separates brain tissue from peripheral circulation and plays a major role in maintaining the brain's microenvironments by preventing the entry of exogenous harmful substances into the brain [6] (Figure 1). Although the BBB is a great hurdle for drug delivery into the brain [7], the integrity of the BBB has been found to be impaired in AD [8]. Unexpectedly, the developed medicines for AD have still not met the clinical expectations; hence, the BBB may be not the primary reason for drug treatment failure.

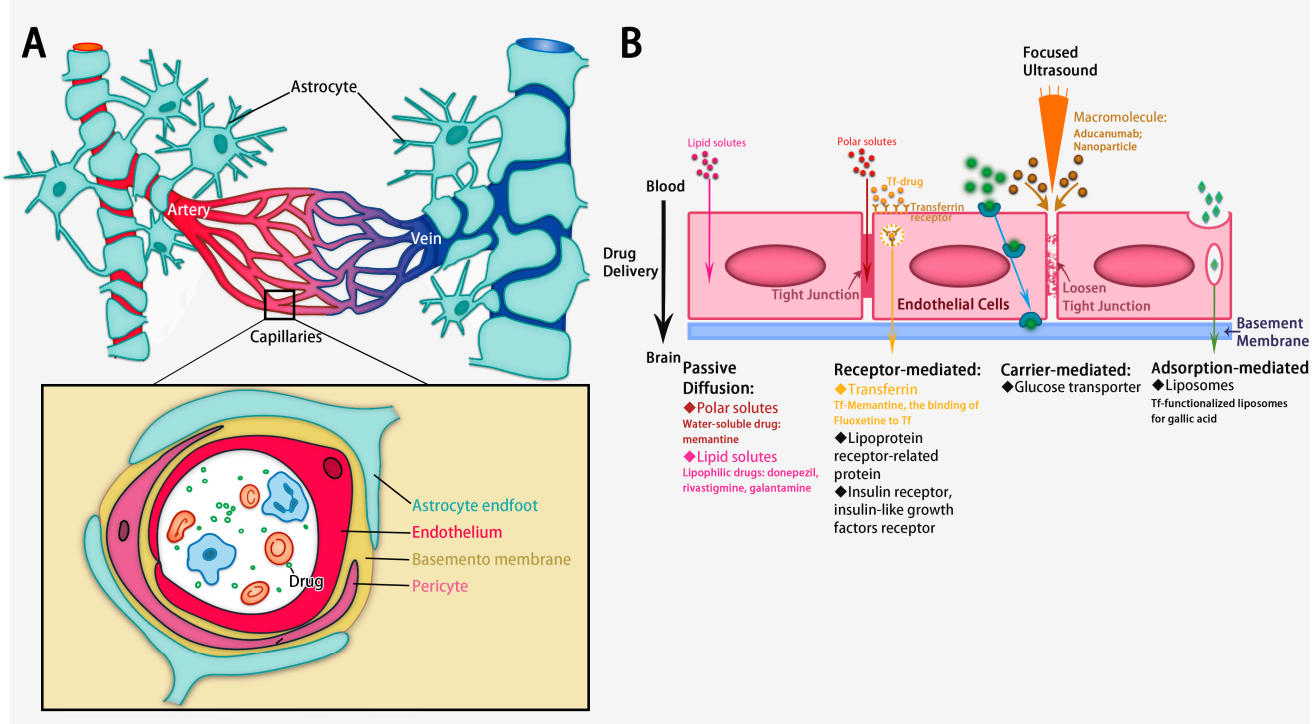

Figure 1. (**A**) The structure of the blood–brain barrier. (**B**) Alzheimer's drug delivery to the BBB (Several ways to increase the AD drug delivery cross BBB. Focused ultrasound increases delivery of aducanumab [9]. Transferrin (Tf) increases delivery of memantine [10] and fluoxetine [11]. Tf-functionalized liposomes increase brain delivery of gallic acid [12]).

The brain extracellular space (ECS) is a narrow gap between brain cells and neighboring cells, which account for approximately 20% of brain volume [13]. The ECS consists of interstitial fluid (ISF), the extracellular matrix (ECM) and other secretory molecules. Neurons and glial cells exchange substances and information in the ECS. The width of the ECS is only 38–64 nm; thus, medicines need to be smaller than this width in diameter in order to cross through the ECS [14]. The main function of ISF is to remove metabolic waste, provide nutrients, and act as a crucial medium for drug delivery [15]. Owing to the separation of dense myelinated fiber bundles, interstitial fluid drainage in the normal brain is regional. It may be difficult for medicines to reach effective concentrations in certain brain regions [16]. Studies have shown that formaldehyde induces Aβ misfolding and oligomerization [17] and senile plaques in extracellular space [18]. Notably, Aβ-related SP deposition in the extracellular space has been proven to slow down or stop ISF drainage in AD, thus actually blocking delivery into the brain [18,19] (Figure 2).

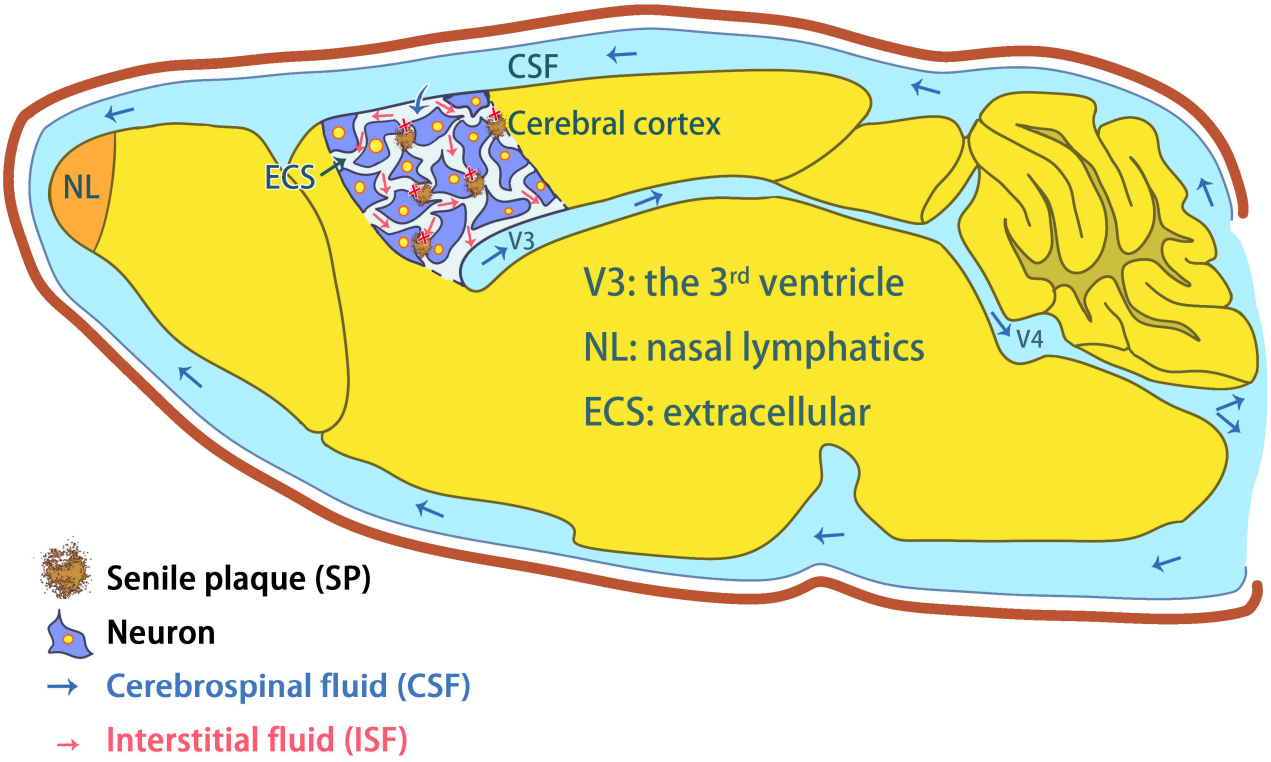

Figure 2. Interstitial fluid (ISF) drainage flows from the superficial cortex and then deep into the brain to the 3rd ventricle pouring into the cerebrospinal fluid (CSF). Finally, CSF flows into nasal lymphatics (NL) where the substances are exchanged with blood [18]. Formaldehyde-induced Aβ deposition in the ECS blocks the exchange between ISF and CSF.

2. Developed Drugs Targeting Aβ and Tau for AD Therapy

Despite the huge investments in drug development, currently, only seven drugs for AD treatment have been approved for marketing by the Food and Drug Administration (FDA) [20,21]. These drugs fall into three categories: cholinesterase inhibitors, NMDA receptor antagonists, and antiβ amyloid (Aβ) monoclonal antibodies. Five of these drugs are used for symptomatic treatment, including donepezil, rivastigmine, galantamine, memantine, and a combination of memantine and donepezil. Recently, the remaining two drugs, Aducanumab and Lecanemab, were designed to be applied in the etiologic treatment of AD [22,23]. Disappointingly, compounds, peptides, and antibodies developed to target Aβ production, aggregation, and elimination as well as tau phosphorylation and aggregation have not met clinical expectations [24].

2.1. Drugs Targeting Aβ

Recently, antiamyloid therapies are a key research focus in terms of the therapeutic principle related to the Aβ cascade hypothesis. This hypothesis suggests that the deposition of Aβ in the brain is the main reason for AD occurrence. The 37–43 amino acid of Aβ is produced by its precursor, the β-amyloid precursor protein (APP). Three protease activities, those of α-, β-, and γ-secretase, are involved in Aβ generation [25]. The nontoxic Aβ monomer has several physiological functions [26]. For example, it is used in APP knockout mice to reduce Aβ-induced weight loss, abnormal muscle and neuronal development, and the number of neurotransmitters [27]. However, $A\beta_{42}$ overloads are associated with the imbalance between Aβ production and clearance [28]. $A\beta_{42}$ aggregation contributes to the formation of soluble Aβ oligomers (AβO) and insoluble Aβ protofibrils, the principal component of senile plaques (SPs) [29]. Toxic soluble Aβ oligomers induce neuroinflammation, cause dendritic spines of neuronal injury and inhibit long-term potentiation [30,31]. Remarkably, Aβ plaques cause neuronal death and memory impairment by blocking the

ECS and ISF flow [18]. Aβ deposition also induces cerebral amyloid angiopathy and further exacerbates cognitive impairments [32,33]. In addition, Aβ induces tau phosphorylation through the PAX6 signaling pathways [34]. At present, the most developed drugs for AD treatment are antiamyloid drugs. For example, Aducanumab and Lecanemab have been approved for clinical treatment for AD patients [22,23].

2.1.1. Drugs Used to Reduce Aβ Production

According to the different sites of APP digestion, the drugs used to reduce Aβ production fall in three categories: β-secretase inhibitors, γ-secretase inhibitors and modulators, and α-secretase activators.

β-secretase (BACE1) is one of the key enzymes for Aβ production. However, the development of β-secretase inhibitors often does not meet clinical expectations (Table 1). *Verubecestat*, a BACE1 inhibitor, was once considered a promising AD drug as it was found to reduce Aβ levels in the cerebrospinal fluid of rats, monkeys and AD patients in a preliminary study [35]. However, two Phase III clinical studies (NCT01739348 and NCT01953601) were terminated due to their inability to achieve the expected results. These AD patients experienced multiple treatment-related adverse effects, including rashes, falls and injuries, sleep disturbances, suicidal ideation, weight loss, and hair discoloration [36,37]. In addition, studies showed that Verubecestat may lead to accelerated volume reduction in the hippocampus (and other brain regions) in AD patients [38]. β-secretase inhibitors, such as *Lanabecestat*, *Elenbecestat*, *Umibecestat*, and *Atabecestat*, were discontinued due to a lack of clinical efficacy. Although these drugs inhibited BACE1 successfully, they did not improve cognitive functions in AD patient because BACE1 cleaves substrates for various functions, especially in neuron cell excitability regulation and axonal myelination [39]. Hence, the inhibition of BACE1 leads to many adverse effects and even exacerbates cognitive function deterioration.

γ-secretase inhibitors (GSIs) face a similar dilemma to that faced by β-secretase inhibitors (Table 1). Poor effectiveness and harmful side effects are the main reasons why these medications have been discontinued. For example, the γ-secretase enzyme cleaves more than 140 substrates, including APLP1 and APLP2, Notch, ErbB4, and p75 [40]. Reducing the hydrolysis of these substrates leads to a variety of adverse reactions. For example, *Semagacestat* leads to a deterioration in cognitive function, skin cancer, an increased risk of infection, and gastrointestinal bleeding by reducing Notch signaling [41]. *Avagacestat*, another γ-secretase inhibitor, also causes multiple adverse reactions, including nonmelanoma skin cancer and gastrointestinal symptoms [42]. As γ-secretase inhibitors increase the risk of cancer and cause cognitive decline, they may be an inappropriate target for the clinical treatment of AD [43]. The γ-secretase modulator (GSM) can selectively inhibit $A\beta_{42}$ production without affecting the total amount of Aβ produced and Notch signaling. *Tarenflurbil*, a GSM, showed success in Phase II RCTs [44]. However, further RCTs on it ended due to its lack of efficacy and adverse effects including dizziness, anemia and infection after treatment [45].

α-secretase inducers increase APP hydrolysis to produce nonamyloid proteins. sAPPα, the cleavage fragments of APP, are involved in neurotrophic and neuroprotective functions [46]. Drugs may act through different signaling cascades to activate ADAM10 (α-secretase A Disintegrin and Metalloprotease 10, and α-secretase in neurons) and stimulate the cleavage of nonamyloid proteins [47]. Disulfiram induces the expression of ADAM10, reduces levels of Aβ plaques in the dentate gyri of AD mice and improves behavioral deficits [48]. Bryostatin1, a macrolide antitumor agent, reduces Aβ40 and Aβ42 in AD mice brain effectively and increases sAPPα secretion in AD patients [49]. Two Phase II RCTs of it finished. Cognitive enhancement was observed in advancing AD patients not receiving Memantine [50]. Acitretin, a synthetic retinoid, stimulates ADAM10 promoter activity and increases CSF sAPPα levels in patients with mild to moderate AD [51]. Epigallocatechin gallate (EGCG), a natural polyphenolic flavonoid, increases α-secretase cleavage activity and improves the cognitive function of APP/PS1 mice [52–54]. Additionally, EGCG

leads to a reduction in neuroinflammation [52] and plays a crucial role in neuroprotection and prevention of Alzheimer's disease [55]. A Phase 2/3 clinical trial of EGCG was recently completed, but no results have been published. There are a variety of natural compounds, including Cryptotanshinone [56,57], Ligustilide [58], Bilobalide [59,60] and Curcumin [61,62], that facilitate the activation of ADAM10 with potential neuroprotection in vivo.

Table 1. Alzheimer drugs targeting β-secretase, γ-secretase and α-secretase.

Drug Name	Drug Target	Phase	Effect in Clinical Trials	Status	Refs.
Umibecestat (CNP520)	β-secretase	Phase 2/3 (NCT03131453; NCT02565511)	Cognitive function decreased slightly, brain atrophy increased, weight loss	Discontinued	[63,64]
CTS-21166	β-secretase	Phase 1 (NCT00621010)	Reduced Aβ in plasma with long-lasting and well-tolerated effects	Discontinued	[65,66]
LY2811376	β-secretase	Phase 1 (NCT00838084)	Reduced Aβ in CSF *; adverse effects: retinal toxicity	Discontinued	[67]
LY2886721	β-secretase	Phase 1 Phase 2 (NCT01561430)	Reduced Aβ in plasma and CSF *; adverse effects: abnormal elevation of liver enzymes	Discontinued	[68]
AZD3839	β-secretase	Phase 1 (NCT01348737)	Slightly reduced Aβ in plasma at doses that did not disrupt cardiac activity	Completed	[69]
Verubecestat (MK-8931)	β-secretase	Phase 3 (NCT01953601)	Well-tolerated; reduced $A\beta_{40}$ levels in CSF *	Discontinued	[70]
Lanabecestat	β-secretase	Phase 3 (NCT02972658; NCT02783573)	Reduced $A\beta_{40}$ and $A\beta_{42}$ levels in plasma and CSF *	Discontinued	[71]
Elenbecestat (E2609)	β-secretase	Phase 3 (NCT02956486)	Well-tolerated; reduced Aβ levels in plasma and CSF*; reduced BACE1 enzyme activity in CSF *; did not alter BACE1 levels	Discontinued	[72,73]
Atabecestat (JNJ-54861911)	β-secretase	Phase 2 Phase 3 (NCT02569398)	Reduced Aβ levels in CSF * and plasma; adverse effects: cognitive deterioration, and elevated liver enzymes	Discontinued	[74–78]
LY3202626	β-secretase	Phase 2 (NCT02791191; NCT03367403)	Resulted in high blood–brain barrier permeability; reduced $A\beta_{1\text{-}42}$ in CSF *; no reduction in cognitive impairment and tau load	Discontinued	[79,80]
Semagacestat (LY450139)	γ-secretase	Phase 3 (NCT01035138; NCT00762411; NCT00594568)	Reduced the production of Aβ in patients; no reduction in cognitive impairment; adverse reactions: increased risk of skin cancer and infection	Discontinued	[41,81]
Avagacestat (BMS-708,163)	γ-secretase	Phase 2 (NCT00890890; NCT00810147)	Slightly reduced Aβ levels in CSF *; adverse reactions: gastrointestinal symptoms, skin diseases, and non-melanoma skin cancer	Discontinued	[82,83]
Tarenflurbil (R-flurbiprofen)	γ-secretase	Phase 3 (NCT00380276; NCT00380276; NCT00105547)	No reduction in cognitive impairment; adverse effects: dizziness, anemia and infection	Discontinued	[44,45]
PF-06648671 (Pfizer)	γ-secretase	Phase 1 (NCT02407353; NCT02440100)	Well-tolerated in healthy subjects; reduced plasma $A\beta_{40}$ and $A\beta_{42}$ and increased $A\beta_{37}$ and $A\beta_{38}$	Discontinued	[84]
CHF5074	γ-secretase	Phase 2 (NCT01303744)	Reduced inflammatory factor CD40 and TNF-α concentrations in CSF; improved executive function in ApoE4 gene carriers	Inactive	[85]
Bryostatin1	α-secretase	Phase 2 (NCT02431468; NCT04538066)	Reduced Aβ40 and Aβ42 and cognitive impairment	Active, not recruiting	[50]

Table 1. *Cont.*

Drug Name	Drug Target	Phase	Effect in Clinical Trials	Status	Refs.
Isotretinoin	α-secretase	Phase 1 Phase 2 (NCT01560585)	Adverse events in 2/3 participants	Terminated	[47]
EHT0202	α-secretase	Phase 2 (NCT00880412)	No significant effect	Completed	[86]
Acitretin	α-secretase	Phase 2 (NCT01078168)	Significantly increased CSF * APPs-α; safe and well-tolerated	Completed	[51]
Curcumin	α-secretase	Phase 2 (NCT00164749; NCT00099710; NCT01811381)	No effects on cognitive function and CFS * and plasma Aβ levels	Unknown	[47]

* Abbreviations: CSF, cerebrospinal fluid.

2.1.2. Drugs Used to Prevent Aβ Aggregation

Since non-toxic Aβ monomers aggregate to form neurotoxic AβO and SPs [87], some drugs have been established to prevent Aβ aggregation (Table 2). *Tramiprosate* is an orally active natural amino acid with good BBB permeability. By stabilizing the multiligand encapsulation of the $A\beta_{42}$ monomer, it inhibits Aβ oligomers and SP formation in AD mice [88]. Although it did not improve cognition in a treatment group, the results of magnetic resonance imaging (MRI) revealed that it reduces hippocampus atrophy in patients [89]. *Tramiprosate* and its precursor, *ALZ-801*, share a common metabolite, 3-sulfoniopropionic acid (3-SPA), which is associated with anti-Aβ oligomeric activity, good oral bioavailability and brain permeability [90]. *ALZ-801* produces positive biomarker results and improves cognitive functions in AD patients. ALZ-801 treatment is still being carried out in a Phase III RCT currently. The peptide sequence *KLVFF* retards Aβ aggregation and partially dissolves the Aβ oligomer [91]. Some studies have shown that several natural compounds could act as aggregation inhibitors [92], such as Brazilin [93], gx-50 [94], Curcumin [95], Epigallocatechin gallate [96,97], and Ginnalin A [98].

Table 2. Alzheimer drugs used to prevent Aβ aggregation.

Drug Name	Principle	Phase	Effect in Clinical Trials	Status	Ref.
PBT2	Reduction in Aβ aggregation	Phase 2 (NCT01590888)	The higher dose reportedly reduced $A\beta_{42}$ levels in CSF *	Completed	[99,100]
Resveratrol	Anti-oxidant capacity; prevention of amyloid deposition	Phase 3 (NCT01504854)	Reduce cognitive impairment and $A\beta_{42}$ in CSF *; increased $A\beta_{40}$ levels in CSF * and plasma; increased brain volume loss	Withdraw	[101,102]
Alzhemed™ (Tramiprosate)	Inhibit the interaction of Aβ with endogenous glycosaminoglycans	Phase 3 (NCT00314912)	Slowed cognitive decline in ApoE4 homozygotes	Unknown	[89,103]
Epigallocatechin Gallate	Remodel toxic amyloid-beta fibrils	Phase 2/3 (NCT00951834)	No public information	Completed	[47]

* Abbreviations: CSF, cerebrospinal fluid.

2.1.3. Drugs Used to Promote Aβ Clearance

Another treatment strategy for AD patient is Aβ clearance through active and passive immunization (Table 3). After the administration of $A\beta_{42}$ to PDAPP transgenic mice, SP formation was reduced through active immunization [104]. In contrast, passive immunization is achieved through Aβ antibody injection that directly reduces Aβ oligomers and senile plaques (SP). Although Aβ antibodies exhibit SP clearance, they also trigger a local inflammatory response and enhance vascular permeability [105]. Varying degrees of amyloid-related imaging abnormalities (ARIA) including cerebral edema (ARIA-E) and

cerebral hemorrhage (ARIA-H) are developed after Aβ antibody therapy, which may aggravate cognitive impairments in AD patients.

Table 3. Alzheimer drugs to promote Aβ clearance.

Drug Name	Principle	Phase	Effect in Clinical Trials	Status	Refs.
Aducanumab (BIIB037)	Passive immunity	Phase 3 (NCT02484547; NCT02477800; NCT01677572)	Bound to soluble monomeric Aβ and reduce brain Aβ; reduced cognitive impairment only at the highest dose; adverse reactions: ARIA *	Approved	[106–108]
Lecanemab (BAN2401)	Passive immunity	Phase 3 (NCT04468659; NCT03887455)	Reduced markers of amyloid in early AD * Alleviated cognitive and functional decline; adverse reactions: ARIA *, infusion-related reactions	Approved	[20,109,110]
Remternetug (LY3372993)	Passive immunity	Phase 3 (NCT05463731)	No public information	Recruiting	https://www.clinicaltrials.gov/ (accessed on 28 March 2023)
Gantenerumab (RO4909832)	Passive immunity	Phase 3 (NCT04339413; NCT04339413; NCT02051608)	No reduction in cognitive impairment; adverse reactions: ARIA *	Terminated	[111,112]
Solanezumab (LY2062430)	Passive immunity	Phase 3 (NCT02760602; NCT01900665; NCT01127633)	Did not significantly affect cognitive decline	Terminated	[112,113]
Crenezumab (MABT5102A)	Passive immunity	Phase 3 (NCT03491150; NCT03114657; NCT03114657)	Did not reduce cognitive decline in participants with early AD *	Terminated	[114,115]
Donanemab (LY30028123)	Passive immunity	Phase 2 (NCT03367403)	Improved cognition and daily living ability in early AD patients; reduce amyloid plaque levels and overall tau load	Recruiting	[116–120]
ABvac40	Active immunity	Phase 1 (NCT03113812)	Good safety and tolerance; triggered a consistent and specific immune response	Unknown	[121]
ACI-24	Active immunity	Phase 2 (2018-000445-39)	Produced a low IgG antibody response, increased CSF * $A\beta_{40}$ and $A\beta_{42}$ levels but caused no change in amyloid-PET.	Completed	https://www.clinicaltrialsregister.eu/ (accessed on 28 March 2023)
Amilomotide (CAD106)	Active immunity	Phase 2 Phase 3 (NCT00795418)	Unexpected changes in cognitive function, brain volume loss, and body weight loss	Terminated	[122]
UB-311	Active immunity	Phase 2 (NCT03531710; NCT03531710)	A slower rate of increase in ADAS-Cog in mild AD * patients; 100% responder rate	Completed	[123]

* Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; ARIA, amyloid-related imaging abnormalities.

Aducanumab is a fully human IgG1 monoclonal antibody with high affinity for the Aβ conformational epitope. It received accelerated approval from the FDA in June 2021 [124]. In transgenic mouse models of AD, Aducanumab enters into the brain and reduces soluble and insoluble Aβ levels. It also decreases brain Aβ deposition in patients with prodromal or mild AD [106]. Previous studies showed that it produced the most favorable effects among all Aβ monoclonal antibodies according to Phase III RCT results [107]. However, 41.3% of trial participants experienced ARIA during the trial period. A total of 1% to 2% of patients required hospitalization or experienced long-term side effects [108].

Lecanemab is a human IgG1 monoclonal antibody targeting protofibrils of soluble Aβ aggregates. In January 2023, the FDA granted accelerated approval for it. Preclinical trials

have shown that it may protect neurons and decrease the amount of Aβ protofibrils in CSF [125,126]. In treatment groups, the treatment group has a 29.7% slower decline in Alzheimer's disease composite scores (ADCOMS) at 18 months compared to the placebo group. However, approximately 12.6% developed cerebral edema and 26.4% of participants experienced infusion-related reactions [109,110]. A recent Phase III clinical trial showed that 18 months of treatment with it slowed the CDR-SB decline rate by approximately 27% and lessened the accumulation of tangles in the medial temporal lobe. Two-thirds of the treatment group became PET-Aβ-negative at 18 months [20].

Although these two Aβ antibodies have been approved, the developed drugs for the Aβ antibody encounter failure. The first generation antiAβ antibodies *Bapineuzumab* and *Solanezumab* did not improve clinical outcomes in mild to moderate AD. RCTs of *Crenezumab* and *Gantenerumab* ended for similar reasons. *Donanemab* is a humanized IgG1 monoclonal antibody that recognizes Aβ (p3-42), the N-terminal pyroglutamate of Aβ in amyloid plaques [117]. It decreases SPs rapidly and continuously in phase 1b [118]. In a Phase II RCT, it showed improvement in cognitive performances and daily activities in early AD patients [119].

2.2. Drugs Targeting Tau Protein

Tau proteins are the most abundant microtubule-associated proteins which are mainly distributed in neuronal axons and the cytoplasm [127]. In the normal brain, tau proteins help to form neurons, stabilize microtubules, and regulate anterograde transport by kinesin and neurotransmitter release. The tau hypothesis suggests that hyperphosphorylated tau proteins interfere with microtubule formation [128], causing microtubule depolymerization, neuronal synaptic dysfunction, and NFT formation. In a brain with Alzheimer's, modifications of tau proteins' aberrant glycosylation facilitate the subsequent hyperphosphorylation of tau [129].

Initially, studies of antitau drugs were focused on tau aggregation inhibitors and microtubule stabilizers (Table 4). However, the failure of most of them may have been due to their high toxicity or low efficacy. *TRx0237* (LMTX™) is a tau aggregation inhibitor. Its active ingredient methylthionine chloride (MTC) binds selectively to abnormal tau proteins and removes damaging tau tangles. Although it has undergone two Phase III RCTs, neither yielded positive primary results [130]. The microtubule stabilizer, *TPI-287*, causes severe hypersensitivity reactions in AD patients [131].

Another research focus in antitau therapy is the clearance of tau proteins through active or passive immunity (Table 4). One of the active immunotherapies is achieved through tau vaccine injection. The most outstanding tau vaccine, *AADvac1*, has undergone Phase II clinical trials with desirable safety and effective immune response [132]. Although improvements in cognitive functions were observed in a subgroup of patients with confirmed AD biomarker profiles, the vaccine did not slow cognitive decline in the whole study sample [133].

Table 4. Alzheimer drugs targeting tau protein.

Drug Name	Principle	Phase	Effect in Clinical Trials	Status	Ref.
TRx0237 (LMTM)	Inhibit Tau aggregation	Phase 3 (NCT01689233; NCT01689246; NCT02245568)	Did not significantly affect cognitive decline	Active, not recruiting	[130]
TPI-287	microtubule stabilizer	Phase 1 (NCT01966666)	Severe hypersensitivity reactions	Completed	[131]
Tilavonemab (ABBV-8E12)	Passive immunity	Phase 2 (NCT03712787; NCT02880956)	Did not change the decline of cognitive, or lower brain atrophy or levels of plasma neurofilament light	Discontinued	[134]

Table 4. *Cont.*

Drug Name	Principle	Phase	Effect in Clinical Trials	Status	Ref.
BIIB076 (NI-105)	Passive immunity	Phase 1 (NCT03056729)	Reduced half the amount of mid-region-bearing tau in CSF *	Discontinued	[135]
Gosuranemab (BIIB092)	Passive immunity	Phase 2 (NCT03352557)	Lack of efficacy	Discontinued	https://www.clinicaltrials.gov/ (accessed on 28 March 2023)
Semorinemab (RO07105705)	Passive immunity	Phase 2 (NCT03289143; NCT03828747)	Caused 43.6% slowed decline in the ADAS-Cog11 coprimary, and did not change tangle accumulation	Active, not recruiting	https://www.clinicaltrials.gov/ (accessed on 28 March 2023)
Bepranemab (UCB0107)	Passive immunity	Phase 2 (NCT04867616)	No drug-related adverse events or changes in safety results were reported	Active, not recruiting	[136,137]
Zagotenemab (LY3303560)	Passive immunity	Phase 2 (NCT03518073)	Missed its primary endpoint	Discontinued	[138,139]
JNJ-63733657	Passive immunity	Phase 2 (NCT04619420)	Dose-dependent reductions in free p217 tau in CSF * in volunteers. Adverse reactions: back pain and headache	Recruiting	https://www.clinicaltrials.gov/ (accessed on 28 March 2023)
AAD-vac1	Active immunity	Phase 2 (NCT02579252)	Reduced brain atrophy and cognitive decline in mild to moderate AD * patients; reduced the levels of p-tau181 and p-tau217	Completed	[132,133,140]
ACI-35	Active immunity	Phase 1 (NCT04445831)	Developed antitau IgG and IgM antibodies preferentially against phosphorylated tau, with high IgG titers	Active, not recruiting	[141]

* Abbreviation: AD, Alzheimer's disease; CSF, cerebrospinal fluid.

Intravenous administration of antitau monoclonal antibodies reduces pathological tau protein levels through passive immunization. However, these tau antibodies fail to achieve the desired outcome. *Gosuranemab*, *Tilavonemab*, and *Zagotenemab* were discontinued after failure in Phase II RCTs, and *Semorinemab* and *Bepranemab* are still active in the development process.

2.3. Drugs Targeting Calcium Balance and Reactive Oxygen Species

Disrupting calcium homeostasis is a prominent feature of Alzheimer's disease [4,142]. Several drugs targeting calcium ions (Ca^{2+}) have entered clinical trials. *Memantine*, which targets the NMDAR receptor, is approved by the FDA for the treatment of moderate to severe dementia in patients with AD. *Memantine* prevents neuronal excitatory toxicity caused by excessive Ca^{2+} [143]. Drugs targeting AMPAR include *LY451395* [144], *LY450108* [145] and *S 18,986* [146], which can regulate Ca^{2+} penetration and reverse memory deficits in mice while no efficacy in cognitive improvement in AD patients are observed. The compound *Tg-2112x* protects neurons by reducing mitochondrial Ca^{2+} uptake, thereby preventing neurodegeneration and the development of dementia [147]. *Multi-target 1,4-dihydropyridines* show calcium channel blockade for AD therapy [148].

Reactive oxygen species (ROS) have been found to accelerate AD pathogenesis [149]. Several natural compounds show good antioxidant capacity. *Astaxanthin (AST)* is a potent exogenous carotenoid that can scavenge superoxide anion radicals. *AST* slows memory decline and decreases levels of Aβ and tau proteins in mice [150]. As an antioxidant neuroprotector, *AST* improves the presynaptic and postsynaptic protein markers associated with memory in APP/PS1 mice [151]. *Crocin* increases the levels of glutathione peroxidase and superoxide dismutase and reduces ROS and $A\beta_{1\text{-}42}$ in the brain of mice [152]. *Linalool*, a monoterpene, decreases the levels of oxidative stress in AD model flies and rats [153].

2.4. New Hypotheses and Drug Targets for AD Treatments

Failures in AD drug developments via Aβ and tau have led to the controversy in the hypothesis of AD pathogenesis and the choice of drug targets. The most important challenge is to determine which endogenous factor directly induces Aβ aggregation and tau phosphorylation in AD. Recently, it has been proven that age-related endogenous formaldehyde is the direct trigger for Aβ- and tau-related pathology. Eliminating formaldehyde can reduce Aβ and tau aggregation and improve memory [154]. This suggests that excessive formaldehyde may be a novel target for AD therapy.

2.4.1. Exogenous Formaldehyde Directly Induces AD-Like Pathology

Gaseous formaldehyde (FA) is widely known as an irritating toxic gas in the environment, and is particularly common in industrialized production. Certainly, occupational exposure to FA or FA solution injection can impair cognitive functions associated with hippocampal neuron death [155]. In particular, formaldehyde induces pathological manifestations similar to those in AD patients in animal brains. Formaldehyde exposure directly causes spatial memory deficits in mice accompanied by hippocampal neuron death [156] (Figure 3). Some early AD-like changes, including cognitive deficits associated with Aβ plaques and tau hyperphosphorylation, have been observed in wild-type mice after acute FA exposure [157]. Intracerebroventricular (i.c.v.) injection of formaldehyde directly induces memory impairments in young rhesus monkeys associated with SP and NFT appearance [158] (Figure 3). In addition, pathological concentrations of formaldehyde impair cognitive function by interfering with DNA methyltransferases and reducing global DNA methylation [159].

2.4.2. Age-Related Endogenous Formaldehyde Induces Memory Decline

Endogenous formaldehyde is a metabolite in the human body. During aging, the imbalance in FA metabolism leads to FA accumulation and neuron death in the brain's age-related memory decline [160]. Further, clinical investigations have demonstrated that age-related formaldehyde concentrations and memory loss are positively correlated in the elderly [161–163]. An increased expression of semicarbazide-sensitive amine oxidase (SSAO, a formaldehyde-generating enzyme) and the decline expression and activity of formaldehyde dehydrogenase (FDH, a formaldehyde degrading enzyme) have been proven to contribute to endogenous formaldehyde accumulation [164]. Overexpression of SSAO in the blood leads to an increase in urinary FA levels in AD patients [162]. FA and Aβ in the CSF of rhesus monkey macaques are positively correlated with age [165,166]. Brain formaldehyde levels were gradually elevated in mice during normal aging, especially, in AD model mice [167].

2.4.3. Formaldehyde Elicits Aβ Oligomerization and Fibrillation

Excessive levels of the endogenous formaldehyde crosslinked nontoxic Aβ monomer promote the formation of toxic Aβ dimers, oligomers and fibrils in vitro [17]. Notably, they also increase the formation of Aβ oligomers and Aβ-related SPs associated with memory deficits in AD model mice [154]. There is direct evidence that methanol (a precursor of formaldehyde) can be oxidized to form formaldehyde in rhesus monkey brains [168]. Feeding rhesus monkeys with methanol causes an increase in the formation of SPs and sustained memory impairments [169]. Aβ also interferes with formaldehyde metabolism. For example, Aβ inactivates the FDH by binding with it, leading to formaldehyde accumulation; in turn, formaldehyde promotes Aβ oligomerization and SP formation in AD model mice [154] (Figure 3).

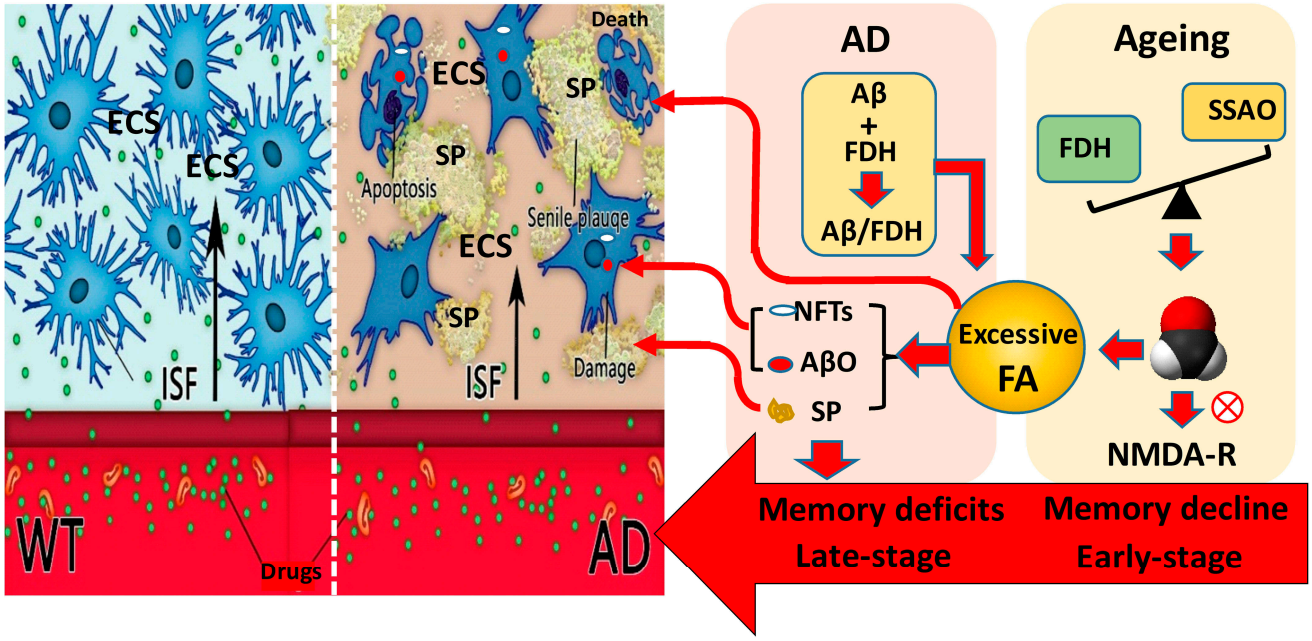

Figure 3. Novel pathogenesis, drug target and delivery in AD. Briefly, aging induces endogenous formaldehyde accumulation by disrupting FDH and SSAO expression [170,171]. Excessive formaldehyde can directly induce neuron death and cognitive decline by inhibiting NMDA receptor [172]. Especially, both age-associated formaldehyde and Aβ-inactivated FDH-derived formaldehyde elicit the formation of intracellular AβO and NFTs and extracellular SP [18,173,174]. Formaldehyde-induced Aβ deposition in ECS blocks ISF drainage and drug delivery [18].

2.4.4. Formaldehyde Promotes Tau Hyperphosphorylation and NFTs Formation

Excessive formaldehyde has been proven to elicit tau hyperphosphorylation and NFT formation via glycogen synthase kinase 3β catalysis in vitro and in vivo [173,174]. After chronic i.c.v. injections of formaldehyde, tau protein phosphorylation was observed in the hippocampus, entorhinal cortex and prefrontal cortex of rhesus macaques [158]. After feeding them with methanol for 6 months, the levels of tau protein phosphorylation on residues T181 and S396 were increased in the CSF of rhesus monkeys. Meanwhile, NFTs were also widely distributed in the brains [169].

2.4.5. Endogenous Formaldehyde as a Target for AD Therapy

The above studies suggest that excessive endogenous formaldehyde directly elicits Aβ- and tau-related pathology associated with hippocampal neuron death. Thus, scavenging formaldehyde may be a potential and new method for treating AD.

Coenzyme Q10 (CoQ10), is a vitamin-like substance that plays significant roles in the energy supply process. It has been revealed that 30 nm nanopacked Q10 (which enhances water solubility) reduces the formation of Aβ plaques and NFTs associated with improved cognitive functions in APP/PS1 mice by directly scavenging formaldehyde [154]. In addition, Q10 also reduces oxidative stress, Aβ production and intracellular Aβ deposition in the cortex of mice with a progerin 1 mutation [175].

Resveratrol, a natural formaldehyde scavenger, reverses formaldehyde accumulation and noradrenaline deficiency. Resveratrol can also improve LTP and memory functions in SAMP8 mice [176]. It also attenuates Tau hyperphosphorylation induced by formaldehyde in N2a cells [177]. Resveratrol reduces Aβ and p-tau pathology in the hippocampus of AD transgenic mice [178] and enhances cognitive functions in AD patients [102]. However, the low water solubility of resveratrol limits its clinical application [179], and nanopacked methods have shown a promising prospect for AD treatments [180,181].

Epigallocatechin gallate (EGCG), a catechin of plant origin, is primarily found in green tea. EGCG make a spontaneous reaction with formaldehyde at room temperature (25 °C) in vitro [182]. A large number of studies support the viewpoint that EGCG has potential neuroprotective effects in neurological diseases including AD [183]. EGCG also activates the Nrf2 signaling pathway and reduces formaldehyde-induced oxidative stress [184]. EGCG reduces Aβ deposition and phosphorylated tau and improves learning and memory in AD mice [185–187]. Although the low water solubility of resveratrol limits its clinical application, the nanopacked method has shown a promise prospect for AD treatments.

Hydrogen Sulfide (H_2S), a signaling molecule, is associated with several systemic diseases, including AD [188,189]. A study found that sodium hydrosulfide, a donor of H_2S, markedly scavenges formaldehyde, increases hippocampal brain-derived neurotrophic factor expression, and alleviates cognitive deficits in formaldehyde-exposed rats [190]. H_2S reduces $A\beta_{1\text{-}42}$ production by inhibiting APP expression promoted by exogenous ATP [191], and improves cognitive function in AD models [192–194]. Whether this gaseous molecule has clinical effects for AD is unclear.

2.4.6. Formaldehyde-Degrading Enzyme-ALDH2 as a Target for AD Treatments

Aldehyde dehydrogenase 2 (ALDH2, a formaldehyde-degrading enzyme) is expressed at the highest levels in the liver, kidneys, muscles and the heart, while it is less expressed in the brain [195]. ALDH2 genetic polymorphism is associated with many diseases including aortic aneurysm/dissection (AAD), hypertension, liver disease and cancer [196–199]. In alcohol-related diseases, ALDH2-deficient individuals are more susceptible to endogenous formaldehyde [200]. The most common genetic mutation is ALDH2*2 associated with cognitive impairment [201,202]. A meta-analysis has shown that the polymorphic locus rs671 G > A of ALDH2 is a potential risk factor for AD in East Asians. An allele mutation results in inactivated ALDH2 proteins, which may explain why carriers of the AA allele are more likely to develop AD than carriers of the GG allele are [203,204]. Toxic aldehydes accumulated in ALDH2-deficient mice brains induce Aβ plaques and NFT formation associated with cognitive impairments [205,206]. On the contrary, ALDH2 overexpression not only reverses cognitive deficits, but also improves mitochondrial integrity and neuronal survival by reducing aldehyde and Aβ toxicity [207].

Alda-1, an ALDH2 activator, significantly protects neurovascular cells from excessive formaldehyde during AD progression [167]. Alda-1 also protects against Aβ toxicity, neuroinflammation [208], and Aβ-induced mitochondrial geometry anomalies [207].

2.4.7. Formaldehyde-Degrading Enzyme-ALDH2 as a Target for AD Treatments

A previous study revealed that red light at 630 nm can penetrate the skulls of mice, and not only reduces levels of H_2O_2 in the brain, but also activates FDH (a specific formaldehyde-degrading enzyme [164]) and scavenges excessive formaldehyde in the brains. Subsequently, FDH activation by red light can alleviate memory deficits in AD model mice [18,171].

3. Enhancing BBB Penetration for Drug Delivery in AD

Although the BBB is a physical barrier to drug delivery, carrier-mediated transport is the approach through the BBB for small molecules, carbohydrates, amino acids, fatty acids, and ions. Receptor-mediated transcytosis is finding a principal pathway for macromolecules, including proteins and peptides, to enter the central nervous system [209]. In Alzheimer's brains, the structure and function of the BBB are disrupted [210]. Aβ induces astrocyte endfeet retraction leading to neurovascular uncoupling [211,212]. A reduction in pericytes has been observed in the cortex and hippocampus [213], leading to a lower clearance of soluble Aβ in interstitial fluid and accelerated brain pathology changes [214]. Therapeutic drugs tend to be trapped in the enlarged perivascular space, which makes it difficult for them to be diffused through brain ECS to reach injured neurons [8] (Figure 3).

The application of nanopacked medicines facilitates the entry of drugs through the BBB. Several nanomedicines have been developed based on alterations in the BBB during disease. Because the expression of the receptor of advanced glycation endproducts (RAGE) in the microvasculature increases [215], RAGE-mediated transcytosis can be used to deliver drugs to brains with Alzheimer's. For example, an ibuprofen and FK506-encapsulated drug codelivery system (Ibu&FK@RNPs) targeting RAGE inhibits the neuroinflammation caused by the NF-κB pathway [216].

4. Aβ Plaques Deposition in ECS Blocks Drug Delivery in AD

Interstitial fluid (ISF) drainage is necessary for drug delivery to target neurons in the brain. The myelin sheath separates the normal brain into different regions, affecting ISF drainage and causing an uneven distribution of drugs in the brain. For example, ISF in the caudate nucleus flows smoothly without being blocked along myelinated fiber tracts toward the ipsilateral cortex, while ISF flowing in the opposite direction is completely blocked by barrier structures [16].

In 2012, a method to visually detect brain ISF drainage was established. The dynamic process of ISF drainage in rat brains can be imaged by magnetic resonance imaging (MRI) with gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) as the tracer [217]. The diffusion properties of extracellular space (ECS) are usually evaluated in terms of volume fraction (α) and tortuosity (λ), with α being the ratio of the volume of ECS to the total volume of brain tissue, and λ being the ratio of the actual distance between two points to the distance between straight lines. α and λ describe the geometric characteristics of the cases in which the ECS can be used for diffusion; i.e., they describe the magnitude factors that impede the diffusion of molecules. In normal brain tissue, the ECS has a volume fraction of about 20% with a tortuosity of about 1.6 [218]. ISF drainage flows from the superficial cortex and then deep into brain to the 3rd ventricle (V3) pouring into the cerebrospinal fluid (CSF). Finally, CSF flows into nasal lymphatics (NL) where the substances are exchanged with blood [18] (Figure 2). The diffusion function of the ECS is disturbed in pathological conditions. One of the typical AD pathological features is Aβ deposition in brain ECS [219]. Aβ plaques in the ECS impede the drainage of ISF from the superficial to the deeper cortical layers and drive the diffusion of ISF around neurons (in a horizontal direction) [18] (Figure 3). Aβ plaque and glial cell proliferation in AD mice leads to ECS volume elevation and ISF flow restriction [220,221], which make it difficult for drugs to reach the deeper layers of the brain. Meanwhile, toxic metabolite accumulation exacerbates deep neuronal apoptosis or death. This may be a possible explanation for the AD drug development failures over the last hundred years.

5. Novel Drug Delivery for AD Treatments

5.1. Drug Delivery via Brain ECS

Drug delivery via brain ECS involves direct therapeutic drug injection into damaged deep neurons through a specialized catheter, avoiding a route with slow or less ISF drainage which results in reduced drug concentrations and low clinical efficacy (Figure 4A). MRI-guided stereotactic delivery improves the neuroprotective efficiency of drugs [222]. Although it is a promising method for AD drug delivery, this invasive treatment poses the risk of intracranial infection and hemorrhage to patients. Additionally, it requires detailed study of the locations and functions of brain subdivision before a highly precise procedure can be performed.

5.2. Magnetic Nanoparticles

Magnetic nanoparticles (MNPs) can effectively penetrate the BBB and reach specific brain regions when exposed to external magnetic fields [223,224] (Figure 4B). Superparamagnetic iron oxide nanoparticles (SPION) are currently the focus of research, and have the advantages of inherent magnetism, high safety and targeting, and easy access to manufacturing methods [225,226]. For example, Tween 80-modified SPION (Tween-SPIONs), a

kind of MNP, can pass through the BBB in rats and accumulates in large amounts in the cortex near the magnet [227]. In the presence of an external static magnetic field (SMF), insulin-modified NPs can effectively cross the BBB and improve the bioavailability of insulin in the brain [228].

5.3. Near-Infrared Photosensitive Nanomedicines

Near-infrared light (NIR) is an electromagnetic wave between visible light and mid-infrared light. The permeability and low tissue destruction of NIR make it widely used in biological science and related fields, particularly in brain imaging [229] and nanomedicine therapy [230] (Figure 4C). NIR combined with nanomedicine is commonly used in antitumor therapy. For example, a NIR-excitable immunomodulating nanophotosensitizer has been developed as an effective and precise antitumor immunotherapy [231]. NIR-based phototherapy, a nanoplatform of the brain-targeting peptide RVG conjugated with the 2D porphyrinic PCN-222 metal–organic framework and indocyanine green (PCN-222@ICG@RVG), has been established for inhibiting Aβ aggregation by NIR irradiation [232]. Local photothermal heat facilitates the photo-oxygenation process of generating oxidized Aβ monomers with low aggregation capability [232]. Human serum albumin-stabilized gold nanoclusters (AuNCs@HSA) have been found to inhibit Aβ aggregation, oxidize Aβ monomers, and attenuate Aβ-mediated neurotoxicity through photo-oxidation under NIR laser irradiation [233].

5.4. Combination of Focused Ultrasound and Nanomedicines

Focused ultrasound therapy is characterized by high tissue penetration and submillimeter steerable focusing. MRI-guided low-intensity focused ultrasound (FUS) serves to induce the BBB to open safely, noninvasively, transiently and centrally in the human hippocampus and internal olfactory cortex [234]. Some studies have revealed that increases in brain interstitial fluid and lymphatic drainage and the opening of the BBB by FUS reduce Aβ plaques [235,236]. FUS applied with microbubbles (FUS^{+MB}) is a novel technique used to breach the BBB and increase drug delivery. After FUS^{+MB} treatment, the delivery of two therapeutic AD antibodies, Aducanumab and RNF5, increases significantly [237].

FUS allows nanomedicines to be released in a specific brain region (Figure 4D). For example, an albumin-based nanocluster and the FUS facilitate the opening of the BBB, allowing the nanocluster to enter the ECS. After localization of drug using MRI, a second FUS will release the nanocluster into the brain tissue [238]. Another method of the embedded combining quercetin modified sulfur nanoparticles (Qc@SNPs) into microbubbles (MB) construct a Qc@SNPs-MB nanosystem. FUS helps to release drugs embedded in microbubbles and cross the transiently opened the BBB, thus improve the abilities of learning and memory in AD mice [239].

5.5. Extracellular Vesicles

Extracellular vesicles (EVs) are particles that are naturally released from cells [240]. It was found that tumor-derived EVs can breach an intact BBB during brain metastasis [241]. Rabies viral glycoprotein-tagged exosomes derived from Mesenchymal stem cells (RVG-tagged MSC-Exo) decrease plaque deposition and Aβ and prevent memory deficits in APP/PS1 mice [242].

5.6. BBB Shuttle Peptide

The BBB shuttle peptide is used to increase the ability of adeno-associated virus (AAV) vectors to cross the BBB [243]. A study showed that the PB5-3 peptide increased AAV9 transport and transendocytosis efficiency [244].

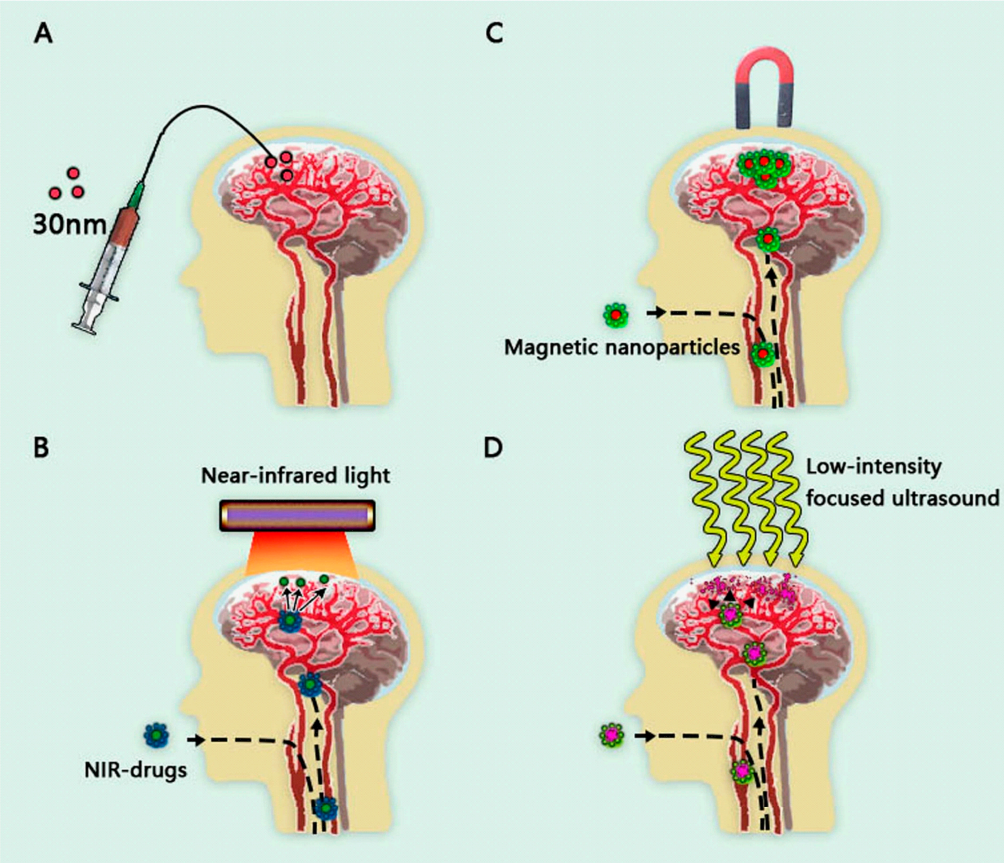

Figure 4. Direction of drug development for Alzheimer's disease. (**A**). Drug delivery via brain ECS. (**B**). Magnetic nanoparticles [223]. (**C**). Near-infrared photosensitive nanomedicines [230]. (**D**). Combination of focused ultrasound and nanomedicines [238].

6. Conclusions and Outlook

For the past two decades, many Alzheimer's disease drug candidates have failed in trials. Although these drugs showed some successes in cellular and animal model experiments, they did not improve cognitive functions in clinical Alzheimer's patients. Aβ monoclonal antibodies reduce Aβ levels in brains with adverse reactions, especially ARIA. Aβ deposition in blood vessels, brain extracellular space, an impaired BBB and blocked ISF drainage cause low efficacy drug delivery. This leads to the lack of therapeutic efficacy in AD drugs. Therefore, there is an imperative need for new therapies that increase BBB permeability and ISF drainage. Encouragingly, red light, near-infrared and focused ultrasound have been proven to enhance ISF drainage in brain ECS [18,235,245].

Even though drug delivery via brain ECS increases precision, it carries infection and intracerebral hemorrhage risks. The noninvasive, low toxicity and high targeting characteristics of physical therapy, nanomedicines with NIR and/or focused ultrasound are considered to be the promising methods. In addition, endogenous formaldehyde is proposed to be a direct endogenous factor in intracellular Aβ oligomerization, NFT formation, and Aβ deposition in ECS in AD. Red light therapy at 630 nm can activate FDH to degrade formaldehyde, smash Aβ plaques, increase ISF flow to deep into the brain, and improve cognitive functions in AD models [18]. Thus, nanopackaged medicines targeting formaldehyde for reducing SP, and new physical methods for accelerating ISF drainage may be the promising strategies for clinical AD therapy.

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