Review

Formaldehyde toxicity in age-related neurological dementia

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ABSTRACT

The primordial small gaseous molecules, such as: NO, CO, H2S and formaldehyde (FA) are present in the brains. Whether FA as well as the other molecules participates in brain functions is unclear. Recently, its pathophysiological functions have been investigated. Notably, under physiological conditions, learning activity induces a transient generation of hippocampal FA, which promotes memory formation by enhancing N-methyl-D-aspartate (NMDA)-currents. However, ageing leads to FA accumulation in brain for the dysregulation of FA metabolism; and excessive FA directly impairs memory by inhibiting NMDA-receptor. Especially, in Alzheimer’s disease (AD), amyloid-beta (Aβ) accelerates FA accumulation by inactivating alcohol dehydrogenase-5; in turn, FA promotes Aβ oligomerization, fibrillation and tau hyperphosphorylation. Hence, there is a vicious circle encompassing Aβ assembly and FA generation. Even worse, FA induces Aβ deposition in the extracellular space (ECS), which blocks the medicines (dissolved in the interstitial fluid) flowing into the damaged neurons in the deep cortex. However, phototherapy destroys Aβ deposits in the ECS and restores ISF flow. Coenzyme Q10, which scavenges FA, was shown to ameliorate Aβ-induced AD pathological phenotypes, thus suggesting a causative relation between FA toxicity and AD. These findings suggest that the combination of these two methods is a promising strategy for treating AD.

1. Introduction

The primordial small gaseous molecules, such as: NO, CO, H2S, which can be synthesized in the brain, and participate in long-term potentiation (LTP) and memory formation (de Cabo and Diaz-Ruiz, 2020; Motterlini and Otterbein, 2010; Wallace and Wang, 2015). Gaseous formaldehyde (FA MW=30) was one of the first organic molecules containing C, H, and O elements to appear during the early formation of the earth (Canuto et al., 1983; Pinto et al., 1980). Methanediol is a product of the hydration of FA and likely the main specie in water. However, it is not clear whether this happens in cells, and how stable is this alcohol, which might be in equilibrium with FA. Endogenous FA (also named active FA) was found to be derived from the demethylation of sarcosine by sarcosine dehydrogenase (SARDH) in the brains (Scott et al., 1970). It is an active aldehyde in the gas phase, but rapidly (the half-time of the hydration reaction is 70 ms) reacts with water to form an inactive alcohol, methylene glycol (Priha et al., 1996).

Actually, FA is the primary precursor of most complex organic molecules, including amino acids, RNA, DNA, and proteins (Robertson and Miller, 1995). It is notoriously known as a pollutant of indoor air that induces memory deficits in animals (Lu et al., 2008) and cognitive decline in humans (Kilburn Kh Fau - Warshaw et al., 1987). Surprisingly, FA is present in every vertebrate cell as a possible byproduct of several metabolic reactions (e.g., methanol oxidation, DNA or histone...

Abbreviations: ADH5, alcohol dehydrogenase 5; ALDH2, aldehyde dehydrogenase 2; ALKB, Alpha-ketoglutarate-dependent dioxygenase; AD, Alzheimer’s disease; Aβ, amyloid-beta; AβO, Aβ oligomers; ApoE, apolipoprotein E; BBB, blood-brain barrier; C, cysteine; C1, one-carbon; CAT, catalase; CSF, cerebrospinal fluid; Chat, choline acetyltransferase; CoQ10, coenzyme Q10; CrT1, creatine transporter-1; CK, creatine kinase; D, aspartic acid; ECS, extracellular space; FD, familial AD; FA, formaldehyde; Glu, glutamic acid; ISF, interstitial fluid; MS-HPLC, liquid chromatography-tandem mass spectrometry; LTP, long-term potentiation; MTHFR, methylene-tetrahydrofolate reductase; NFTs, neurofibrillary tangles; NMDA-R, N-methyl-D-aspartate receptor; P450, cytochrome p450; PD, Parkinson’s disease; Q, glutamine; ROS, reactive oxidative species; SARDH, sarcosine dehydrogenase; SD, sporadic AD; SSAO, semicarbazide-sensitive amine oxidase; SPs, senile plaques; GSNOR, S-nitrosoglutathione reductase; SHMT1, serine hydroxymethyltransferase-1.

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2. Metabolism of endogenous FA

2.1. Pathways that generate endogenous FA

FA is endogenously generated by multiple pathways of enzyme-mediated demethylation, which can involve sarcosine dehydrogenase (SARDH) in the mitochondria (Ai et al., 2019; Porter et al., 1985; Wittwer and Wagner, 1981); the cytoplasmic serine hydroxymethyltransferase-1 (SHMT1) (Morellato et al., 2021; Wan, 2016), semicarbazide-sensitive amine oxidase (SSAO) in the blood, vessel, muscle and adipose tissue (Yu et al., 1997); monoamine oxidase in the blood, liver, kidney and brain (Xu et al., 2018; Yu et al., 1994); and nuclear DNA/RNA demethylase (Kalasz, 2003; Trewick et al., 2002; Wan, 2016), lysine-specific histone demethylase-1 (LSD1) (Shi et al., 2004), Alpha-ketoglutarate-dependent dioxygenase (ALKB) (Trewick et al., 2002), and Jumonji histone demethylases (Morellato et al., 2021). Other sources of FA have been found. For example, some specific foods can cause FA to rise abnormally by more than 0.33 mM in the body (Kalasz, 2003). In addition, some medicines and environmental pollutants (for example: methylmercury) can produce FA through mitochondrial cytochrome p450 (P450) activity (Kalasz, 2003) (Fig. 1a).

2.2. Pathways that degrade FA

Endogenous FA is utilized by participating in a “one-carbon cycle” or alternatively metabolized by FA-related enzymes in vivo. On the one hand, FA in cells is metabolized through ADH5 (Burgos-Barragan et al., 2017; Staab et al., 2009); on the other hand, it is degraded into formic acid and water, which are excreted in the urine (Teng et al., 2001). Endogenous FA is mainly degraded by glutathione-dependent FA dehydrogenase (mouse ADH-3, human ADH-5, also named S-nitrosoglutathione reductase, GSNOR) (Pontel et al., 2015; Rizza et al., 2018), alcohol dehydrogenase 1 (ADH1), and glutathione-independent aldehyde dehydrogenase 2 (ALDH2) (Teng et al., 2001). In addition, catalase (CAT) also contribute to the degradation of FA (Harris et al., 2003). Naturally, FA participates in a cross-linking reaction with DNA and proteins (Fig. 1b).

3. Endogenous FA dually regulates memory

3.1. Nervous excitation induces FA generation and axonal transport

Recently, to address the critical question of how FA is endogenously generated in the hippocampus, stimulating electrodes and recording electrodes were filled with a mitochondrial FA probe (mito-FA-probe, green) (Fig. 2a), and then high-frequency electrical stimulation was applied to evoke an action potential. The results showed that endogenous FA was rapidly generated in the mitochondria of the cultured hippocampal neurons. At the same time, mitochondria-derived FA (green) was rapidly transported or spread along the axons of the neurons (Ai et al., 2019) (Fig. 2b). These data indicate that this small molecule, FA (MW=30), as well as nitric oxide (NO, MW=30), could act as a...
3.2. Endogenous FA regulates both LTP and memory

Endogenous FA has been found to bidirectionally regulate hippocampal LTP (Ai et al., 2019; Tong et al., 2013a). Further, FA is considered to be a memory-related molecule in mice and humans, based on the following facts. On one hand, learning-activity-derived FA promotes the formation of LTP and spatial memory by activating NMDA-receptor (NMDA-R) via the C232 residue of the NR2B subunit (Fig. 2c). On the other hand, high concentrations of FA inhibits NMDA-R by cross-linking the C79 residue of the NR1 subunit and the K79 residue of the NR2B subunit (Fig. 2d).

3.3. Age-related accumulation of FA directly impairs memory in animals

Brain FA has been found to be gradually accumulated in the brains of healthy male mice during the aging process from 6 to 24 months. Similarly, hippocampal FA levels at 8 months were higher than those at 3 months in rats (Tong et al., 2013b). Remarkably, both intraperitoneal injection and intrahippocampal infusion of FA into healthy adult rats mimicked age-related memory decline in aged rats (Tong et al., 2013a).

Injection of FA into healthy adult Sprague Dayle rats to duplicate the detected concentration in the aged rats has been found to impair hippocampal LTP formation in these aged rats (Mei et al., 2015), and directly damage memory by inhibiting NMDA-receptor (Ai et al., 2019). Hence, age-related FA accumulation directly damages synaptic functions and cognition.

3.4. Age-related increases in FA levels impair human cognition

A previous clinical investigation was carried out using 425 healthy human blood samples and 65 urine samples, and revealed that blood FA levels gradually increased during the aging process and, in particular, a significant elevation occurred at 70 years of age (Tong et al., 2013b). Another clinical survey of 604 elders and 517 patients showed that there was a positive correlation between urine FA levels and the degrees of cognitive decline (Tong et al., 2017; Yu et al., 2014). These data suggest that the abrupt elevation in FA content in 70-year-olds is the critical endogenous factor that induces cognitive decline in the elderly and dementia patients.

4. Disorders of FA metabolism are related to sporadic dementia

4.1. Abnormality in FA metabolism-related enzymes induces dementia

Documented evidence has shown that the disorders of FA metabolism-related pathways lead to cognitive impairments or dementia (Fig. S1).

4.1.1. FA-transforming enzymes: CK, CrT1, GAMT

Creatine transporter-1 (CrT1) and creatine kinase (CK) mainly transfer creatine into the mitochondria and form sarcosine (a FA precursor) (Scott et al., 1970). Surprisingly, supplementation of creatine can transiently increase hippocampal FA levels (Ai et al., 2019; Souza et al., 2012) and temporarily improve cognitive performance in mice and humans (Rae et al., 2003). However, excessive FA impairs cognitive function in mice and rats (Ai et al., 2019). Consistently, polymorphisms or knockout of CrT1 and CK lead to cognitive impairments in mice or humans (Aksenova and Burbaeva, 1989; Kurosawa et al., 2012; Streijger et al., 2005; Udobi et al., 2019). Guanidinoacetate methyltransferase (GAMT) deficiency induces similar symptoms of mitochondrial encephalopathy (Morris et al., 2007).

4.1.2. FA-generating enzymes: SARDH and SSAO

Clinical investigations have found that SARDH mutation leads to a low intelligence quotient (IQ) in children (Scott et al., 1970). Further study found that SARDH knockout induces a deficiency in hippocampal FA and memory deficits in mice associated with low activation of the NMDA-receptor; similarly, 11 children with a SARDH mutation exhibit cognitive impairments (Ai et al., 2019). Notably, abnormally high levels of blood SSAO have been found in patients with vascular dementia and AD (Yu, 2001). The levels of SSAO in the serum were also positively correlated with FA levels and cognitive decline in stroke patients (Tong et al., 2017; Yu et al., 2014).

4.1.3. FA-degrading enzymes: ADH-3 and ALDH2

Under physiological conditions, FA is mainly degraded by GSH-dependent FDH (also named mice ADH-3, or human ADH-5) (Dingler et al., 2020; Umansky et al., 2021), which is strongly expressed in the
white matter and moderately expressed in gray matter. ADH-3 can help to prevent age-related neurodegeneration (Mori et al., 2000). However, GSH concentrations were shown to decrease significantly in the different brain regions of the aged rats (Zhu et al., 2006). A low level of brain GSH is thought to be one of the causes of neurodegenerative diseases (Gironi et al., 2011). The decreased GSH levels in aged rat brains are related, at least in part, with diminished de-novo synthesis of GSH with a low activity of gamma-glutamylcysteine synthetase. This biosynthetic pathway is important for GSH balance in all cell types.

Notably, ADH5 activity varies from 12- to 30-fold in different tissues; for example, the liver, kidney, stomach, and intestine have the highest activity, while the brain, heart, lung, and testis have the lowest activity (Uotila and Koivusalo, 1997). ADH5 gene polymorphism is common and associated with dementia (Li et al., 2006; Thomasson et al., 1991). Knockdown of ADH5 genes resulted in significantly reduced FA tolerance in mice (Oeltzou et al., 1999). Unsurprisingly, ADH5 deletion leads to memory deficits (Ai et al., 2019).

When FA levels are too high in the body, the GSH-independent ALDH2 plays a more important role in degrading FA than ADH-3 (Dicker and Cederbaum, 1986; Oka et al., 2020). The Km constant for FA degradation by ALDH2 is 0.5 mM, which is higher than that for ADH-3 (Km = 0.3 mM) (Mukerjee and Pietruszko, 1992). ALDH2 polymorphism is closely related to dementia (Kamino et al., 2000; Wang et al., 2008). And a mutation in the ALDH2 gene reduced FA degradation by 10% (Wang et al., 2002). ALDH2 knockout mice showed significant memory deficits (Ohsawa et al., 2008). In fact, inhibition of ADH5 and ALDH2 led to FA accumulation and memory impairments (Tong et al., 2013a, 2013b).

4.1.4. Enzymes interfering with FA metabolism: CAT and MTHFR

When brain GSH is depleted, catalase (CAT) becomes the main enzyme that degrades FA. CAT polymorphism has been detected in dementia patients (Goulas et al., 2002). A decline in this enzyme activity leads to memory impairments (Manrique et al., 2005).

In addition, methylene-tetrahydrofolate reductase (MTHFR) polymorphism impairs the one-carbon (C1) metabolism in AD patients (Durman et al., 2019); induces FA accumulation (Thornride and Beck, 1977), and leads to cognitive disorders (Andrew H Ford et al., 2012; Mansoori et al., 2012).

4.2. Multiple factors-derived FA accumulation impairs cognitive functions

Epidemiological surveys have shown that the occurrence ratios of SD and FD in total dementia are about 95% and 5%, respectively (Hampel and Lista, 2012; Tong et al., 2017). Therefore, discovering which endogenous factor contributes to the onset of sporadic dementia is an issue of particular concern. Numerous studies have shown that multiple exogenous and endogenous factors (Fig. 3a), such as age (Qiang et al.,...
5. Endogenous FA is a critical trigger of Aβ aggregation and toxicity

5.1. FA accumulation in AD models and patients

5.1.1. FA overload in APP/PS1 mice

In a previous study amyloid-beta (Aβ) senile plaques (SPs) appeared in the hippocampus and cortex of APP/PS1 mice (a familial AD mouse model with double London/Swedish mutations) and were consistently accompanied by a rapid elevation in hippocampal FA and a gradual increase in cortical FA levels at 3, 6, and 9 months (Yue et al., 2019) (Fig. 3c). A critical evidence is that Aβ levels in the brains of R1.40 APP transgenic mice at different ages are maintained at a relatively stable concentration; however, at longer times there is greater Aβ accumulation can induce stress in the endoplasmic reticulum via SIRT-1 (Li et al., 2012) and impair the mitochondrial respiratory functions during the aging process in vitro induced unsaturated aldehyde generation in vitro (Breitner et al., 1988). Of note, the levels of Aβ generation in vitro (Barelli et al., 2008; Milligan, B.a.H, 1980). These data suggest that making Aβ monomers have no neurotoxicity (Rozga and Bal, 2010). Notably, Aβ monomers induced by FA were isolated (Fig. 3d). In addition, Aβ in the central nervous system is more difficult to degrade than that in the peripheral organs (Xiang et al., 2015). Therefore, the artificial “aged Aβ” is toxic to neuron and impairs cognitive functions. It is widely known from in vitro experiments that the solutions of Aβ monomers under a stationary condition do not readily self-aggregation. Furthermore, to replicate “aged Aβ”, at least 3-days of violent shaking are required to promote Aβ oligomerization and fibrillation in vitro (Xiang et al., 2015) (Fig. 3d).

5.1.2. FA accumulation in AD patients

Clinical investigations have shown that FA levels in the urine, blood, and hippocampal autopsy samples of 141 CE patients were markedly higher than 50 age-matched controls. In particular, the urine FA levels were positively correlated with the degrees of dementia in AD patients (Heck et al., 1982; Zhiqian Tong et al., 2011).

5.1.3. FA overload associated with ADHS abnormality

Ageing induces a decline in the expression and activity of ADHS (a FA-degrading enzyme) while an increase in these two features of SSAO (a FA-generating enzyme), which is associated with a marked increase in the levels of brain FA, but not the peripheral liver FA levels (Mei et al., 2015; Qiang et al., 2014; Zhiqian Tong et al., 2011). Specifically, upon intraperitoneal injection of exogenous Aβ solution, Aβ-mediated SP was only depositd in the brains of APP23 transgenic mice, but not in the peripheral organ (liver) after 4 months (Eisele et al., 2010). This may be because ADHS activity in the central nervous system is markedly lower than that in the peripheral organs (Uotila and Koivusalo, 1997). Another explanation may be that Aβ directly affects ADHS activity (Fig. 3d). In addition, Aβ in the central nervous system is more difficult to degrade than that in the peripheral organs (Xiang et al., 2015).

5.2. Aβ-inactivated ADHS induces FA accumulation in vivo

Aggregation of the Aβ peptide, which is cleaved from APP, contributes to the pathogenesis of late-onset AD (Hardy and Selkoe, 2002). The most common variants of Aβ are 40 (Aβ40) and 42 (Aβ42). Although Aβ42 is expressed at a much lower level than Aβ40, it shows higher cell toxicity and has been found to be the initial and major component in cerebral SPs (Wolfe, 2002). In most late-onset AD cases, the disease appears to occur at an average age of 65 years (Reitz et al., 2020). Recently, Aβ42 has been found to bind with human ADHS (PDB: 1MC5, containing catalytic Zn²⁺ and structural Zn²⁺) (Fig. 4a, 4b). Theoretically, the first residue- aspartic acid (D1) of Aβ42 is connected with the 96th residue- glutamine (Q96) of ADHS, which is interconnected with the 97th residue- cysteine (C97 in the structural Zn²⁺) by using molecular simulation. Aβ-induced structural alteration of ADHS leads to its inactivation (Fig. 4c). Further evidence showed that Aβ disassembles the active tetramer ADHS to form the inactive dimer ADHS (Fig. 4d), which results in a low activity of ADHS and an elevation in intracellular FA levels in the cultured cells and APP/PS1 mice (Yue et al., 2019). In fact, abnormal high levels of hippocampal FA were also found in AD patients (Zhiqian Tong et al., 2011).

5.3. Aβ oxidative demethylation induces FA generation in vitro

Notably, Aβ monomers have no neurotoxicity (Rozga and Bal, 2010). However, the artificial “aged Aβ” is toxic to neuron and impairs cognitive functions. It is widely known from in vitro experiments that the solutions of Aβ monomers under a stationary condition do not readily self-aggregation. Furthermore, to replicate “aged Aβ”, at least 3-days of violent shaking are required to promote Aβ oligomerization and fibrillation in vitro (Rozga and Bal, 2010). It is not clear which chemical reaction promotes oligomerization during shaking process or which molecule crosslinks Aβ monomers to elicit self-aggregation.

Previous studies showed that FA can induce the aggregation of Aβ40 and Aβ42 in vitro (Chen et al., 2007; Teng et al., 2001). Indeed, several proteins during the aging process in vitro induced unsaturated aldehyde generation in vitro (Barelli et al., 2008; Milligan, B.a.H, 1980). These data suggest that making “aged Aβ” induces FA generation in vitro. Remarkably, Aβ42 contains two serine residues (S5 and S26) with the exposed hydroxymethyl groups (-CH2-OH); other amino residues are relatively more stable than these two hydroxymethyl residues (Fig. 5a), which can produce FA by oxidative demethylation (Fei et al., 2020; Kalasz, 2003; Li et al., 2012). In fact, oxidative demethylation of Aβ at S5/26 induced a time-dependent in FA generation, which can be detected by three different methods, including: FA probe, FA kit, and HPLC (Fig. 5b). Especially, mutations in these two S residues lead to reduce FA generation in vitro (Fei et al., 2020). Hence, the oxidative demethylation of Aβ by violently shaking leads to FA production.

5.4. FA cross-links Aβ monomer to form Aβ dimer and other aggregations

Recently, the Aβ dimer (two molecules of Aβ) has been found to induce neuronal dysfunction in the early stage of AD (Zott et al., 2019) and provide the “seed and nucleus structure” to form Aβ oligomers (AβO) and fibrils in the late stage of AD (Ahmed et al., 2010; Bernstein et al., 2009; Shankar et al., 2008). Of note, the levels of Aβ dimer, more than other oligomers, were positively correlated with the degree of dementia of AD patients (Lesne, 2014). However, the precise mechanism of how two molecules of Aβ monomer form Aβ dimer is unknown.

Monomeric Aβ has no neurotoxicity, while the violently shaken monomeric Aβ solution induced the formation of the “aged Aβ” and neurotoxicity (Rozga and Bal, 2010). Which factor induces the self-aggregation of Aβ monomer during this shaking process is unclear. Previous studies showed that FA is a critical crosslinker for Aβ aggregation in vitro (Chen et al., 2006; Yue et al., 2019). Recently, it has been found that FA cross-linked with the K28 (lysine, K) residue in the β-turn of Aβ monomer promotes the formation of Aβ dimers, oligomers, and fibrils (Figs. 5b, 5c).

The crosslinking target K28 residue of the Aβ dimer induced by FA can be detected by liquid chromatography- tandem mass spectrometry (MS-HPLC), and the structures of Aβ isoforms induced by FA were identified by atomic force microscope and scanning transmission electron microscope. However, Aβ42 mutation at the K28 residue, or scavenging of FA, completely abolished Aβ aggregation in vitro. Especially,
FA injection indeed enhances the formation of intracellular Aβ oligomers (recognized by A11 antibody) and extracellular SP (stained by Th

5.5. FA elicits rapid Aβ assembly in early-onset AD

Notably, several Aβ mutations lead to the emergence of AD symptoms before the age of 65 years, and the resulting disease is known as early-onset familial AD (Wu et al., 2012). Mutations clustering near the Aβ N-terminus can alter Aβ production and enhance the kinetics of fibril and intermediate aggregate species formation (Hori et al., 2007; Yang et al., 2018), while mutations located at the Aβ C-terminus are shown to affect the release of Aβ by accelerating its production (Suzuki et al., 1994; Zhou et al., 2011). Particularly, the mutations reported within residues 21–23 of Aβ are implicated in not only increasing Aβ production but also enhancing Aβ aggregation kinetics and/or delaying Aβ clearance (Grabowski et al., 2001; Nilsberth et al., 2001). Furthermore, FA has been found to accelerate Aβ oligomerization and fibrillation in Aβ mutants (including A22G, E22K, and D23N) compared with wild-type Aβ (Fei et al., 2020; Krone et al., 2008). Notably, both FA and Aβ dimer levels are positively correlated with severity of dementia in AD patients (Lesne, 2014; Tong et al., 2017; Zott et al., 2019). These indicate their synergistic roles in promoting Aβ deposition and AD occurrence (Fei et al., 2020).

5.6. A vicious circle involving FA generation and Aβ deposition

Previous studies have shown that the process of aging leads to a gradual accumulation of FA in the brains of mice, rats, and humans (Mei et al., 2015; Tong et al., 2013a, 2013b), due to imbalances in both the activity and expression of SSAO and ADH5 (Qiang et al., 2014). Intrahippocampal infusion of a precursor molecule of FA, methanol, promoted Aβ-related SP formation and short-term memory decline in monkeys (Yu et al., 2014; Zhai et al., 2018). Exposure to gaseous FA also significantly increased the levels of Aβ and hyperphosphorylated tau, activated microglia, impaired the blood–brain barrier (BBB), and damaged spatial memory in wild-type mice (Liu et al., 2017).

Previous study indicated that age-related FA levels were elevated in AD patients and cross-linked with the arginine 112 and 158 residues of apolipoprotein E (ApoE). This may provide a reasonable explanation for why ApoE genetic variation and aging are two of the most noted risk factors associated with the development of AD-related dementia (Rizak et al., 2014).

In addition, some microRNAs (miR), including miR29 and miR485, can reduce Aβ generation in AD patients (Amakiri et al., 2019). However, FA was found to reduce the expression of miR29 and miR485 (Li et al., 2015; Rager et al., 2013). These data provide a clue that FA may promote the production of Aβ via miR, which needs to be investigated in the future.

More importantly, FA directly induced tau phosphorylation and aggregation to form neurofibrillary tangles (NFTs) by activating the GSK/PP2A pathway (He et al., 2016; Lu et al., 2013; Nie et al., 2007a, 2007b). Mitochondrial damage and tau hyperphosphorylation have been found in patients with sporadic and/or genetic dementia (Gandbhir and Sundaram, 2020; Luna-Munoz et al., 2005).

FA-derived from exogenous and endogenous factors initiates cognitive impairments in sporadic/familial dementia. Especially, in familial dementia, age-associated FA and Aβ-derived FA rapidly promote AD onset by accelerating Aβ aggregation and tau hyperphosphorylation. A vicious circle is formed between Aβ-induced FA accumulation by inactivating ADH5 and FA-promoted Aβ deposition by triggering Aβ oligomerization and fibrillation (Yue et al., 2019) (Fig. 3d). Special attention is to be noted that age-related FA can directly cause cognitive decline by promoting tau hyperphosphorylation and inhibiting NMDA-R (Ai et al., 2019; Lu et al., 2013; Nie et al., 2007a, 2007b). This also gives a possible explanation why AD drugs only targeting Aβ did not reach the expected therapeutic effects in these decades.
5.7. FA enhances Aβ-induced cellular toxicity

Substantial evidence shows that FA impairs brain functions (Rana et al., 2021), induces the generation of reactive oxidative species (ROS) by inhibiting the caspase-dependent apoptotic pathway (Carla Umansky et al., 2020; Zhang et al., 2010). Aβ also can promote ROS generation (Pratico, 2008). However, it has been found that FA synergistically worked with Aβ to promote ROS generation by enhancing Ca^{2+} influx, and reduce ATP generation by suppressing COX activity and reducing coenzyme Q10 levels in the mitochondria, which finally induced neuron death (Fei et al., 2020) (Fig. 6).

6. Lessons from medicine development failures for treating AD

6.1. Neglected nervous structures – the “brain ECS”

Most of the research in brain science has been focused on neural networks and vascular systems, which account for 80–85% of the total brain mass. However, the remaining brain extracellular space (ECS) systems (15–20%) have not received much attention over the past 100 years. Notably, the roles of “extracellular space” should not be neglected, because it may play a crucial role in brain structure and function (Fenstermacher J, 1988; Godin et al., 2017; Tonnesen et al., 2018). Actually, the nano-scale structures of these ECS (diameter = 38 – 64 nm), which exist in the narrow gaps between inter-connected and irregular interstitial tissues, are an important link between neurons and glial cells, and also an essential functional unit for maintaining homeostasis of the brain cell living environment (Stern, 2016) (Fig. 7a). In particular, the interstitial fluid (ISF) in the ECS contains neurotransmitters, hormones, nutrient substances, and metabolic wastes; ISF drainage has been found to affect sleep and cognition (Fenstermacher J, 1988; Lei et al., 2017; Xie et al., 2013). However, there have been few reports on ISF drainage in the nano-scale ECS of brains thus far.

6.1.1. Drug delivery failure in AD

Drugs that are developed for brain diseases, such as stroke, AD, Parkinson’s disease (PD), brain tumors etc., first need to penetrate the BBB. Then, they must pass through the 38–64-nm diameter ECS to approach the neurons in the deep layer of the cortex along the direction of ISF drainage. However, it has been reported that 95% of the developed synthetic drugs, antibodies, and synthetic polypeptides did not pass through the BBB (Mansor et al., 2019; Misra et al., 2003), and that drugs of diameter greater than 60 nm did not enter the ECS or arrive at the target neurons (Hoshyar et al., 2016) (Fig. 7b).

The limitations associated with both the BBB and ECS directly or indirectly caused the overall failure of hundreds of billions of dollars of research and development of traditional vascular drugs for encephalopathy (Fisher et al., 2009). Unsurprisingly, the drugs developed for AD treatment targeting Aβ production, aggregation, deposition, or phosphorylation, aggregation of the tau protein, antibodies, compounds, and small molecules have also failed over the past 100 years (Cummings et al., 2018; Mangialasche et al., 2010). More importantly, Aβ-mediated
SP was shown to block the ECS and disturb ISF drainage and led to the death of deep neurons in the cortex in AD. Meanwhile, it may also be the main reason for the failure of the currently developed drugs to enter the nano-scale ECS of the brains of AD patients (Yue et al., 2019) (Fig. 7c).

6.2. Aβ-blocked ECS disturbs Aβ clearance through the ISF and CSF

ISF in the ECS constitutes the microenvironment of neurons and is a direct and critical site for exchanging nutritional, metabolic, and neurotransmitter signals (Lei et al., 2017). The cerebrospinal fluid (CSF) is considered a "reservoir" of ISF because of its extensive interaction with the ISF in the brain. The earliest finding of ECS change in AD was reported in 2005, and it revealed that Aβ deposition in the ECS damaged synaptic transmission and spatial memory in APP23 transgenic AD model mice (Sykova et al., 2005). Further, AβO have been found to flow in the direction of ISF drainage, gradually deposit in the ECS, and impair the synapses (Hong et al., 2014). Therefore, Aβ deposited in the ECS blocks ISF flow and disrupts the exchange of signals between the ISF and CSF (Jessen et al., 2015; Thrane et al., 2014).

6.3. Endogenous FA is essential for Aβ deposition in the ECS

It is known that excessive FA may cross-link two Aβ monomers to form an Aβ dimer (Chen et al., 2006; Gubisne-Haberle et al., 2004). The dimer is a major factor for inducing neuronal hyperactivation in the early stages of AD (Zott et al., 2019). Further, Aβ dimmers had been found to be derived from two molecules of Aβ monomers cross-linked by FA, which can further form AβO and deposit as SP in the later stage of AD (Fei et al., 2020). Subsequently, Aβ-mediated SP blocked the ECS and induced neuron death (Bernstein et al., 2009). Recently, using the visualized method of tracer-based magnetic resonance imaging (MRI) with a Gd-DTPA probe (Gao et al., 2021; Lei et al., 2017; Teng et al., 2018; Wang et al., 2019; Zhao et al., 2020), Aβ-mediated SP has been observed to obstruct ISF flow, which induces the death of deep neurons in the brain and spatial memory deficits in APP/PS1 mice; however, degrading FA and smashing SP by red light at 630-nm can rescue ISF.

Fig. 6. FA enhances Aβ toxicity by promoting Ca²⁺ influx, ATP depletion, and ROS generation in the mitochondria of neurons. Abbreviations: ADH5: alcohol dehydrogenase 5; Aβ: amyloid-beta; AβO channel: channel of Aβ oligomers; APP: amyloid precursor proteins; ATP: adenosine triphosphate; BACE1: beta-site APP cleaving enzyme-1; CcOX: Cytochrome c oxidase; FA: formaldehyde; MPTP: mitochondrial permeability transition pore; Q10: coenzyme Q10; ROS: reactive oxygen species. SP: senile plaques.

Fig. 7. Aβ deposition in ECS blocks ISF flow and drugs delivery into the neurons in the deep layer of the cortex. (a and b) The model of drug-penetrated into BBB and ECS in the brains of healthy humans and AD patients, respectively. (c) Formaldehyde plays a pivotal role in the multiple hypothesis of AD. Abbreviations: Ach: acetylcholine; AD: Alzheimer’s disease; ADH5: alcohol dehydrogenase 5; ADP: adenosine diphosphate; ATP: adenosine triphosphate; Aβ: amyloid-beta; AβO: Aβ oligomers; BBB: blood–brain barrier; CcOX: cytochrome c oxidase; ChAT: choline acetyltransferase; ECS: extracellular space; FA: formaldehyde; Glu: glutamate; ISF: interstitial fluid; Mito: mitochondria; NFTs: neurofibrillary tangles; NMDA-R: N-methyl-D-aspartate receptor; Pi-tau: phosphorylation of tau; Q10: coenzyme Q10; ROS: reactive oxygen species; SP: senile plaques.
obstruction (Huang et al., 2020; Yue et al., 2019) (Fig. 7c and Fig. S2).

6.4. Endogenous FA plays a pivotal role in multiple hypothesis of AD

FA may be a common trigger for AD of these various hypotheses. “Aβ hypothesis” proposed Aβ cascade toxicity (Selkoe and Hardy, 2016). FA can promote Aβ oligomerization and fibrillation (Fei et al., 2020). “tau hypothesis” assumed that tau phosphorylation and aggregation is the final common pathway in AD (Maccioni et al., 2010). FA has been found to elicit tau-related phenotype in vitro and in vivo (He et al., 2016; Lu et al., 2013; Nie et al., 2007a, 2007b). “Ach hypothesis” suggested that reduction of acetylcholine (Ach) levels in the brains lead to AD onset (Ladner and Lee, 1998; Wevers et al., 2000). Consistently, FA can decrease Ach levels by inhibiting choline acetyltransferase (ChAT) (Zhang et al., 2019). “ROS or oxidative stress hypothesis” speculated that oxidative metabolic reactions and their by-products have been consistently implicated in AD pathogenesis (Pratico, 2008). Unsurprisingly, FA can induce oxidative stress (Matsuoka et al., 2010; Silva Macedo et al., 2016). “Aβ/O hypothesis” proposed that it is Aβ oligomers which promote the pathological process in AD patients (Ferreira and Klein, 2011). Recent study showed that FA is essential for cross-linking two molecules of Aβ monomer to form dimer and oligomers (Fei et al., 2020). “Glu hypothesis” considered that glutamic acid (Glu) stimulation induces neuron death in the early stage of AD by activating NMDA-R (Esposito et al., 2013; Hynd et al., 2004). FA has been found to regulate NMDA-currents dually (Ai et al., 2019). “SP-ECS hypothesis” suggested that Aβ-mediated SP in the ECS leads to neuron death in AD (Sykova et al., 2005). Constantly, FA has been found to facilitate Aβ aggregation and block ECS, subsequently, it induces cognitive impairments (Yue et al., 2019). “Virus hypothesis” proposed that infect of Porphyromonas gingivalis in teeth contributes to AD onset; and FA has been found to be accumulated in the teeth (Dominy et al., 2019; Haditches et al., 2020; Koskinek et al., 2007; Rozylko, 1997; Rozylko et al., 2000) (Fig. 7c).

7. New therapeutic strategies for AD

AD is the most common neurodegenerative disorder and the main cause of dementia in the world. Indeed, worldwide, there are over 9.9 million new cases of dementia each year, implying one new case every 3 s. Thus, in the World, nearly 50 million people have Alzheimer’s or related dementia. This number wills almost double every 20 years, reaching 75 million in 2030 and more than 130 million in 2050. Unfortunately, pharmacological therapies targeting Aβ and tau to treat AD have not resulted in desirable clinical efficacy over the past 100 years (Cummings et al., 2018; Mangialasche et al., 2010). Physical therapy is being increasingly investigated as an alternative. A potential strategy for treating AD may involve combining destroying Aβ deposits in the ECS (38–64 nm) through physical treatment with administering oral nano-medicines with diameters less than 38 nm.

7.1. Phototherapy using near-infrared or red light

Some clinical investigations have found that phototherapy with near-infrared light (800–1080 nm) or red light (621, 630, 632, 635, and 680 nm) could improve cognition in AD patients (Berman et al., 2017; Chao, 2019; Maksimovich, 2019; Salehpour et al., 2019a; Saltmarche et al., 2017). However, near-infrared or red light of wavelengths over 650 nm has a strong “heating effect” (Ayyarapetan, 2015; Henderson and Morries, 2015), and sometimes resulted in headaches, sleep disturbance, insomnia, and stroke (Yerman and Terman, 1999). To avoid the heating effect and prevent Aβ-blocking of the ECS (Yue et al., 2019), a 630-nm red light therapeutic device was used to treat AD by destroying the Aβ-mediated SPs (Zhang et al., 2019). By using this equipment to irradiate APP/PS1 mice for 2 months, Aβ/ADH5 complex was disassembled, brain FA was degraded by activating ADH5, Aβ-mediated SPs in the ECS were crushed, which restored the ISF flow and improved spatial memory (Yue et al., 2019) (Fig. S2 and Fig. S3).

7.2. Treatment with nano-packed CoQ10

A clinical survey showed that assessing serum coenzyme Q10 (CoQ10, a liposoluble molecule with low solubility in water) levels may be useful for predicting the development of dementia, rather than as a biomarker for the presence of dementia (Momiyama, 2014). Serum CoQ10 levels were inversely associated with the risk of disabling AD (Yamagishi et al., 2014). Some studies have confirmed the protective roles of CoQ10 in neurodegenerative diseases (Yang et al., 2016). CoQ10 indeed contributes to the treatment of AD (Imagawa et al., 1992). Encouragingly, an enhanced water-soluble nano-Q10 (Muthukumar et al., 2018), or a type of nano-packed Q10 with a 30-nm diameter (Q10, an endogenous FA scavenger) and NaH5SO3 (an exogenous FA scavenger) have been found to degrade FA, reduced intracellular Aβ oligomers and extracellular SPs, and rescued spatial memory in APP/PS1 mice (Fei et al., 2020) (Fig. S2 and Fig. S4).

7.3. Treatment with a combination of phototherapy and nano-CoQ10

Some studies suggest that a combination of phototherapy and nano-Q10 for treating AD may be more therapeutically effective than one of these methods used alone (Hamblin, 2019; Salehpour et al., 2019a, 2019b). According to ECS-controlled ISF drainage in the brain, 630-nm red light not only directly removed blockage of the ECS by SP and restored ISF flow, but also activated ADH5 to degrade FA and reduce Aβ deposition. Red light at 630 nm could also directly reduce tau hyperphosphorylation (Zhang et al., 2019). Moreover, 30-nm Q10 (smaller than the ECS diameter) could enter the ECS and follow the ISF flow into the deep cortical layer to rescue apoptotic neurons (Fei et al., 2020). Hence, the combination of these two methods to accelerate ISF drainage will contribute to drug delivery and the recovery of nerve signals.

8. Concluding remarks and future perspectives

Although medicines in development for AD targeting Aβ have failed for over 100 years (Cummings et al., 2018; Mangialasche et al., 2010), Aβ is a confirmed pathological factor for familial AD patients with APP and/or PS1, PS2 mutations (Bernstein et al., 2009). To work out the mechanisms of why the nontoxic Aβ monomers form the high toxic Aβ dimers and other aggregations will contribute to develop drugs for AD patients.

Generally, FA controls memory formation through two-way regulation of the NMDA-receptor. FA derived from exogenous and endogenous factors directly induces cognitive impairments. In familial dementia especially, FA can cross-link two molecules of Aβ monomer to form dimmers followed by further oligomerization and fibrillation; subsequently, AβO and SP accelerate cognitive decline (Chen et al., 2006; Gubisne-Haberle et al., 2004). There is a vicious circle involving the production of FA and Aβ deposition (Yue et al., 2019). However, scavenging FA could restore cognitive functions by reducing Aβ deposition and tau hyperphosphorylation (Fei et al., 2020). These data indicate that excessive FA is the direct and common trigger for cognitive deficits in sporadic/familial dementia; while APP/PS1/PS2 mutations-derived Aβ is an accelerating factor for FA accumulation and cognitive decline in familial or genetic dementia. Subsequently, familial dementia occurred earlier and rapidier than sporadic dementia. This is a possible explanation of why AD drugs only targeting Aβ did not produce the expected therapeutic effects over the past decades.

Since FA directly impairs cognition in sporadic and familial dementia, the development of medicines that are FA scavengers may contribute to the treatment of AD. The natural FA scavenger resveratrol (Tybik et al., 1998; Zhqian Tong et al., 2011) and endogenous coenzyme Q10 (Fei et al., 2020), have been found to some extent to reduce FA levels and improve memory in APP/PS1 mice. However, the low BBB
penetration of these two compounds and their low water solubility limit their clinical application and therapeutic effects. Nano-packaging could improve their water solubility and liposolubility, and has yielded positive effects in AD model mice (Fei et al., 2020; Moradi et al., 2020; Muthukumarana et al., 2018). Another critical question is whether Aβ deposition in the ECS blocks IF fluid flow in the brain. A blockage certainly makes it difficult for medicines dissolved in the IF to approach the damaged neurons in the deep cortex (Yue et al., 2019). Thus, destroying the non-water-soluble Aβ-mediated SP by physical methods should be a priority strategy for treating AD. Alternatively, the combination of phototherapy and oral nano-Q10 may have a promising therapeutic effect in AD patients.

CRediT authorship contribution statement

Y.D.K., H.Z., and D.H.C.: Conceptualization, Writing – original draft, Writing – review & editing, D.H.C., and H.B.H.: Editing and Funding acquisition; Z.Q.T.: Writing, Review, Editing, and Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no competing financial interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2021.101512.

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