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CURRENT PERSPECTIVES

Iron and Ferroptosis as Therapeutic Targets in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD), one of the most common neurodegenerative diseases worldwide, has a devastating personal, familial, and societal impact. In spite of profound investment and effort, numerous clinical trials targeting amyloid-β, which is thought to have a causative role in the disease, have not yielded any clinically meaningful success to date. Iron is an essential cofactor in many physiological processes in the brain. An extensive body of work links iron dyshomeostasis with multiple aspects of the pathophysiology of AD. In particular, regional iron load appears to be a risk factor for more rapid cognitive decline. Existing iron-chelating agents have been in use for decades for other indications, and there are preliminary data that some of these could be effective in AD. Many novel iron-chelating compounds are under development, some with *in vivo* data showing potential Alzheimer's disease-modifying properties. This heretofore underexplored therapeutic class has considerable promise and could yield much-needed agents that slow neurodegeneration in AD.

Key Words Alzheimer's disease · therapeutics · treatment · iron · chelation · ferroptosis

Introduction

Around 50 million people have dementia worldwide, with nearly 10 million new cases each year. Dementia is one of the leading causes of disability among older people and was the fifth leading global cause of death in 2016. Alzheimer's disease (AD), the most common type of dementia, accounts for about two thirds of cases [1].

Pathologically, AD is characterized by cerebral atrophy, extracellular deposition of amyloid-β peptide in senile plaques, intraneuronal accumulation of hyperphosphorylated tau in neurofibrillary tangles, chronic inflammation, oxidative stress, and loss of neurons and synapses [2]. The predominant pathophysiological model for AD is the amyloid cascade hypothesis, first proposed in 1992 [3]. This posits that the causative and initial pathological event in AD is deposition of amyloid-β, which forms senile plaques. The corollary of the amyloid cascade hypothesis is that anti-amyloid-β therapies should modify the course of AD.

Numerous anti-amyloid therapies, such as β-secretase converting enzyme inhibitors and anti-amyloid-β monoclonal antibodies, lower amyloid in the brain and cerebrospinal fluid, but none these drugs have been shown to delay disease progression [4]. To date, several dozen phase 3 trials have failed to meet primary endpoints. Recently, studies of aducanumab, a monoclonal antibody with promising initial data, were terminated after a futility analysis only to be revived when further data were analyzed in spite of controversy over these results due to the potential of unblinding [5, 6]. Some argue that the use of anti-amyloid-β therapeutics in the symptomatic stage of AD may be too late. This hypothesis is being tested in ongoing trials in presymptomatic amyloid-positive individuals at risk of sporadic AD [7] and in people with mutations in genes associated with dominantly inherited AD [8], but the multiple failures of prior amyloid-β-lowering agents does not bode well for the outcome of these studies. Furthermore, it is well-established that amyloid-β is often present in healthy older brains [9]. These data shed mounting doubt on the validity of the amyloid cascade hypothesis and whether amyloid-lowering therapeutics have any prospect of clinically meaningful efficacy. New aspects of neurodegeneration in AD need to be explored in order to pave the way to disease-modifying therapeutics.

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Iron and Oxidative Stress in the Brain

Of particular interest is the potential role of ferroptosis, a form of nonapoptotic programmed cell death characterized by iron-dependent accumulation of lipid hydroperoxides to lethal levels [10], which has been implicated in a number of neurodegenerative disorders [11, 12].

Iron is an essential cofactor for many physiological functions [13]. The ability to easily gain or lose electrons makes it well suited for metabolic processes, such as the transport and activation of small molecules and electron transfer [13, 14]. The vast majority of the 5 g or so of iron in the body is found in hemoglobin and myoglobin, as well as the storage proteins ferritin and hemosiderin. Only a few hundred milligrams are involved in critical enzymatic processes which capitalize on iron's variable coordination chemistry, permitting it to exist in different oxidation states, including 0, + 2, + 3, + 4, and + 6. Ferrous (Fe^{2+}) and ferric (Fe^{3+}) iron and are the most common in biological systems [13].

The brain has a high demand for adenosine triphosphate (ATP) to maintain membrane ion gradients, synaptic transmission, and axonal transport. Iron is part of cytochromes a, b, and c, cytochrome oxidase, and the iron-sulfur complexes of the oxidative chain, making it essential for ATP production [15]. Iron is also involved in the synthesis of neurotransmitters, as well as lipids and cholesterol, which are substrates for myelin synthesis [14, 16–18]. Although iron is essential for normal brain functioning, it is toxic in the case of overload or dyshomeostasis, which can cause neurodegeneration by disrupting mitochondrial function, depleting ATP, and inducing oxidative damage and chronic inflammation, resulting in damage to lipids, proteins, and DNA [14, 15, 19–22]. Cognition, motor function, dopamine-related functions, and myelinogenesis are commonly affected in CNS iron dysregulation [15].

The ability of iron to undergo oxidation–reduction allows it to convert hydrogen peroxide to toxic free radicals, leading to oxidative stress and cell death via the Fenton reaction, first described in 1894 [14, 23, 24]. When free iron donates an electron to hydrogen peroxide, a hydroxyl radical is produced, which is one of the most reactive free radical species known: $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\cdot}OH + OH^{-}$ [14, 24]. Iron-induced oxidative stress causes a positive-feedback loop of additional iron release from ferritin, heme proteins, and iron-sulfur clusters [14]. Free iron is more likely to exchange electrons with nearby molecules than when protein-bound, leading to further free radical production [14]. When free radicals are generated near membrane phospholipids, they initiate peroxidation of polyunsaturated fatty acids, leading to production of lipid hydroperoxides which break down to form lipid-derived α,β-unsaturated 4-hydroxyaldehydes [25, 26]. Free radical-induced modifications to proteins leads to the addition of reactive carbonyl functional groups, generated from lipid peroxidation, glycation, and amino acid oxidation [27, 28].

Although most models of iron-mediated neuronal injury involve Fenton-mediated hydroxyl radicals, an alternative model posits that depletion of reduced glutathione decreases activity of monothiol glutaredoxins and decreased incorporation of iron into target metalloproteins. This leads to an increase in available iron in the cell, which is diverted to the chaperone poly(rC)-binding protein 1 and hypoxia-inducible factor prolyl hydroxylases (HIF PHDs) in the cytoplasm and nucleus. Increased HIF PHD1 activity results in enhanced transcription of activating transcription factor 4-dependent pro-death genes and induction of ferroptotic death [29].

It is unsurprising that free iron levels are tightly regulated. Iron is generally bound to chaperone proteins in order to control its reactivity, restricting it to specific locations where it cycles between reduced (Fe^{2+}) and oxidized (Fe^{3+}) states as part of physiological processes [30, 31]. In the plasma, iron exists primarily as Fe^{3+} bound to transferrin [14]. The main protective strategy to prevent iron overload in the brain is selective transport systems on the blood–brain barrier [32]. Iron-transferrin complexes circulating in the blood cross the blood–brain barrier via endocytosis mediated by the transferrin receptor (TfR) on the surface of capillary endothelial cells [32]. Iron is then transported from the basolateral membrane of endothelial cells to the cerebral compartment, where it is available to neurons and glia [14]. Nontransferrin-bound iron can enter via lactoferrin receptors [33]. Intracellular free iron exists in the reduced form Fe^{2+}, which acts as a cofactor for iron-dependent enzymes in the cytosol, mitochondria, and nucleus [32]. Intracellular iron levels are controlled by iron-regulatory proteins that bind iron-responsive elements in mRNA [23]. Anti-oxidant defenses inhibit damage caused by free radicals, via the enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) [13, 14], as well as nonenzymatic anti-oxidant substances such as ascorbic acid (vitamin C), alpha-tocopherol (vitamin E), carotenoids, and flavonoids [14].

Brain Iron Is Elevated in Alzheimer's Disease

Accumulating evidence suggests that iron excess and dyshomeostasis contribute to neurodegeneration in AD [12, 32]. Several of the biological abnormalities seen in AD are consistent with free radical damage from impaired iron homeostasis [34].

Iron elevation was first shown in the brains of people with AD in 1953 [35]. Elevated brain iron in AD has been confirmed in numerous subsequent studies both post mortem [36–42] and *in vivo* [36, 38, 42–53]. Iron rises in the brain with aging and may be pathological because it is associated with cognitive decline prior to disease [54, 55]. Increased iron

occurs as early as the mild cognitive impairment stage of AD and contributes to longitudinal outcomes [56, 57]. Iron and ferritin are found within plaques, NFTs, and blood vessels in AD [42]. Although an increase in brain iron levels may contribute to AD pathology, it is excessive iron in specific intracellular compartments or regions of the brain, i.e., regional siderosis, that appears to drive neurotoxicity, particularly in the cortex and hippocampus [14, 36, 42, 58, 59].

Several MRI modalities can be used to image iron levels. T2* MRI allows semiquantitative measurement of brain iron, though the results are influenced by differences in crystal structure, unequal clustering of ferritin, and the size of the magnetic particle [60]. Severity of AD pathology correlates with iron accumulation on postmortem T2*-weighted MRI [61]. Quantitative susceptibility mapping (QSM) is more specific than other MRI modalities as a measure of tissue magnetic susceptibility and correlates well with brain iron levels [62]. QSM imaging demonstrated increased brain iron levels in multiple regions of interest in people with AD compared to controls [63]. QSM also correlates with clinical measures. Higher hippocampal QSM levels predicted accelerated decline in episodic memory, and temporal and frontal QSM levels predicted deteriorating performance on a language task [64]. Magnetic susceptibility in the left caudate also correlated with declining scores on the Mini-Mental State Examination and Montreal Cognitive Assessment in mild and moderate AD [62]. A recent Australian Imaging Biomarker and Lifestyle prospective study found that when brain iron load measured by MRI was compared in normal elderly and mild cognitive impairment (MCI) and AD subjects, brain iron loading was exaggerated in a manner that correlated with cognitive impairment [65].

Brain iron load also impacts longitudinal AD outcomes [66]. Elevated cerebrospinal fluid (CSF) ferritin, a reporter of brain iron burden [67, 68], independently predicted conversion to AD and was associated with poorer cognition and hippocampal atrophy [69]. CSF ferritin levels are associated with disease progression in prodromal people with high amyloid-β pathology determined by CSF t-tau/Aβ42 ratio [70]. High CSF ferritin levels are also associated with accelerated depreciation of CSF Aβ1-42, from threshold preclinical levels to the average level of Alzheimer's subjects, suggesting that iron may facilitate amyloid-β deposition, accelerating the process of AD [71]. Plasma ferritin levels are elevated in cognitively normal amyloid PET-positive older subjects compared to controls with low neocortical amyloid load [72], suggesting that impaired iron mobilization is an early event in AD pathogenesis [72]. The magnitude of impact of CSF ferritin on AD outcomes is commensurate with the tau/Aβ42 ratio, previously one of the best CSF diagnostic biomarkers for AD [73]. CSF ferritin thus appears to be a complementary prognostic biomarker to the t-tau/Aβ42 ratio that predicts near-term disease progression risk [64].

In addition to ferritin, other proteins involved in iron transport correlate with AD symptoms. CSF levels of melanotransferrin, a transferrin homolog that binds iron, are associated with conversion of MCI to AD [74]. Hepcidin is a regulatory protein present in the brain which binds to the iron channel ferroportin, leading to decreased export of cellular iron [75–77]. Serum hepcidin levels are raised in AD and correlate, albeit weakly, with the Clinical Dementia Rating Scale [75]. Although it is possible that the finding of raised serum hepcidin could have been the result of inflammation-based induction of hepatic hepcidin production, values did not correlate with C-reactive protein levels in this cohort, though subjects with levels greater than 5 mg/l were excluded [75]. In the healthy brain, hepcidin and ferroportin are widely distributed and colocalize in neurons and astrocytes, suggesting a role for these proteins in regulating neuronal iron release. In AD brains, hepcidin expression is reduced and anatomical distribution is restricted to neuropil, blood vessels, and damaged neurons [76]. Brain ferroportin levels are also reduced in AD, potentially secondary to ischemia, inflammation, neuronal loss, and senile plaque formation [76]. The reason for reduced hepcidin levels in AD brain are less certain, but reduced passage across damaged vascular endothelium is one possibility [29].

Some potential sources of increased brain iron deposits include bleeding, iron-containing macrophages crossing the blood–brain barrier, and dysregulated blood–brain barrier iron transport [78]. Phagocytic cells containing iron are often present in areas of neurodegenerative changes. These cells may have migrated to these regions in order to phagocytose iron, or iron-containing phagocytic cells may enter the central nervous system as part of an inflammatory response [78]. Lysosomal dysfunction may also be a source of increased CNS iron uptake [78].

Amyloid Precursor Protein in Iron Transport and Oxidative Stress

There is a complex interplay between amyloid-β, tau, and iron in both physiological and pathological states, which can be used to integrate the role of iron into a modified version of the amyloid cascade hypothesis.

Amyloid-β is generated from amyloid precursor protein (APP) [79], a single-pass transmembrane protein with high levels of expression in the brain [80]. APP helps protect cells from iron-catalyzed oxidative stress by loading Fe^{3+} onto transferrin and stabilizing the iron export channel ferroportin [36]. APP knockout mice have decreased ferroportin levels and increased levels of age-related iron accumulation with concomitant oxidative stress in cortical neurons [36]. APP may thus act to oppose brain iron elevation during normal aging [81]. APP levels are modulated by an iron-responsive

element (IRE) in the 5′ untranslated region of the APP transcript [82, 83]. In conditions of high iron, such as Alzheimer's disease, APP translation is increased [84]. Iron regulation of APP mRNA suggests that this could be a target for iron chelators [82]. Intracellular iron chelation increased binding of iron-responsive element-binding protein 1 to the APP IRE, decreasing APP expression [82, 83].

Dysregulation of iron homeostasis is a common effect of mutations in the genes involved in early-onset familial Alzheimer's disease, *PSEN1*, *PSEN2*, and *APP*. PSEN and APP may be involved in regulation of iron homeostasis throughout the aging process [85].

Iron Binds Amyloid and Tau, Promoting Toxicity

Iron binds amyloid *in vitro* [86] with an affinity eight times higher than that in transferrin [87] and is elevated in senile plaques [14, 35]. X-ray microscopy techniques at submicron resolution in the APP/PS1 mouse model of AD showed a direct correlation of amyloid plaque morphology with iron as well as evidence for the formation of an iron–amyloid complex [88]. Magnetite iron species was shown in plaques, suggesting aberrant iron redox chemistry [88]. Quantitative susceptibility mapping compared with flutemetamol positron emission tomography (PET) showed local correlation between β-amyloid plaque and iron deposition in healthy older adults without dementia [89].

Tau, the main component of neurofibrillary tangles, helps mediate iron efflux from cells [90]. High levels of iron colocalize with tau in neurofibrillary tangles [90, 91]. Iron promotes tau hyperphosphorylation by inducing kinases and possibly also by impacting protein phosphatase 2A activity [90, 92]. Iron also causes aggregation of hyperphosphorylated tau [93–95] via an iron-binding motif in the tau protein [90].

Amyloid-β Plaques Are a Site of Redox Activity, Facilitated by Iron

Iron causes amyloid-β aggregation *in vitro* [96–98] and promotes Aβ aggregate toxicity [99–101]. The affinity of amyloid-β for iron increases following aggregation, and further iron binding leads to additional neuronal cytotoxicity [97, 99–104]. Protein carbonyl groups, markers of oxidative damage to DNA and proteins, are seen in preclinical and established Alzheimer's disease [105, 106].

Amyloid-β plaques and neurofibrillary tangles are major sites of redox reactivity, which is catalyzed by iron binding [30, 34, 42, 87, 98]. *In vitro* studies show that amyloid-β captures and reduces Fe^{3+} from the ferritin core, leading to intraneuronal Fe^{2+} elevation [36, 107] and production of hydrogen peroxide. Hydroxyl radicals may then contribute to oxidative damage on both the amyloid-β peptide and surrounding molecules including proteins, lipids, and nucleic acids, with concomitant disruption of membrane integrity [30]. Oxidation also impairs amyloid-β clearance by the low-density lipoprotein receptor-related protein (LRP1) [30]. Elevated levels of Aβ1-40 and Aβ1-42 are associated with increased levels of oxidation products in the AD hippocampus and cortex [108]. Given that iron appears to contribute to amyloid-β-mediated toxicity, it is possible that iron-modifying therapies may have benefit where other modalities of anti-amyloid-β therapeutics have failed.

Iron Overload Impairs Microglia, Increasing Reactive Oxygen Species Production

Iron overload causes microglia to take on a senescent phenotype with reduced motility and altered surveillance. When confronted with injury, they produce a more sustained inflammatory response with increased reactive oxygen species (ROS) production. It is possible that microglia are pushed to a more pro-inflammatory phenotype by age-related changes [109]. Stimulation of cultured microglia with amyloid-β induces an inflammatory phenotype, causing these cells to retain iron, and reduces their phagocytic and chemotactic functioning [110]. Microglia extracted from APP/PS1 mice also have an iron-retentive phenotype with reduced amyloid-β phagocytotic ability [110].

Ferroptosis in AD

Ferroptosis, first described in 2012, is biochemically and morphologically distinct from other forms of cell death such as apoptosis and necrosis and is characterized by iron-dependent accumulation of lipid peroxides [10, 11]. Ferroptosis is induced by the small molecule erastin, which inhibits cysteine import via the cystine-glutamate antiporter system Xc-, leading to depletion of glutathione, a tripeptide formed from cysteine, glutamate, and glycine [10]. Glutathione is a substrate for the selenoenzyme glutathione peroxidase 4 (GPX4), which converts potentially toxic lipid hydroperoxides to nontoxic lipid alcohols [111–113]. Morphological features of ferroptosis include small mitochondria with condensed mitochondrial membrane densities, reduction or vanishing of mitochondrial crista, outer mitochondrial membrane rupture, and electron lucent nuclei [114, 115].

Ferritinophagy may play a critical role in the regulation of ferroptosis [116]. When ferroptosis is induced via cysteine depletion, nuclear receptor coactivator 4 mediates the autophagic degradation of ferritin (ferritinophagy), leading to release intracellular free iron [116]. HER2C, a modulator of

ferritinophagy [116], regulates turnover of FBXL5, which is part of a complex that targets iron regulatory protein 2 for proteasomal degradation and thus appears to play a role in iron metabolism [117]. HERC2 deficiency could induce neurodegeneration by impairing response to increased iron levels, leading to ferritinophagy, release of free iron, and neuronal damage [116].

Erythroid 2-related factor 2 (Nrf2) is a transcription factor that regulates genes involved in the metabolism of glutathione, iron and lipids, and mitochondrial function [118]. Nrf2 may help protect against ferroptosis, and enhancing Nrf2 signalling may hence be neuroprotective [118].

Emerging work suggests that ferroptosis may play a role in AD pathology. Lipid peroxidation levels are elevated in the brain in AD [119, 120]. Mice with a conditional deletion of GPX4 display cognitive impairment and hippocampal degeneration similar to that of AD with neurodegenerative features of ferroptosis (including lipid peroxidation, extracellular signal-related kinase (ERK) activation, and neuroinflammation), which is ameliorated by a ferroptosis inhibitor [121]. Ferroptosis may exacerbate AD by targeting the hypoxia-inducible factor 1α and heme oxygenase-1 pathways [116].

Ferroptosis is modulated by pharmacological perturbation of lipid repair systems involving glutathione and GPX4 [11]. Cell death caused by ferroptosis can be suppressed by iron chelators, lipophilic anti-oxidants, inhibitors of lipid peroxidation, and depletion of polyunsaturated fatty acids [11]. Some ferroptosis inhibitors appear in Table 1 [11].

Studies of therapeutics with potential anti-ferroptosis activity show promise, though there are few data from human studies. Trials of vitamin E supplementation to prevent cognitive decline or treat AD have produced conflicting results [122]. Donepezil-butylated hydroxytoluene hybrids have been designed as potential anti-AD therapies [123]. Studies of idebenone have shown cognitive improvement in AD, but conclusive evidence for a benefit of sufficient magnitude to be clinically significant is lacking [124–126]. In rat models of AD, vildagliptin modulated AD-associated biochemical changes [127], reduced tau phosphorylation, increased the expression of proteins associated with synaptic plasticity in the hippocampus [128], attenuated amyloid-β, and improved memory [129]. Linagliptin mitigated cognitive deficits, as well as attenuating amyloid-β, tau phosphorylation, and neuroinflammation in a 3xTg-AD mouse model [130]. In cultured human neuronal cells, linagliptin alleviated amyloid-β-induced mitochondrial dysfunction and intracellular ROS generation [131]. Studies of deferoxamine and deferiprone in AD are discussed below. Baicalein improved cognition decreased amyloid-β and prevented tau phosphorylation in AD mouse models [132, 133]. PD-146176 preserved memory, lowered amyloid-β, decreased tau pathology, and reduced autophagy in a 3xTg mouse model of AD [134, 135]. Zileuton improved memory and reduced amyloid-β and tau pathology in 3xTg AD mice [136, 137]. A small randomized controlled pilot trial of supra-nutritional sodium selenate in AD showed that subjects whose CSF selenium concentrations raised with treatment had reduced deterioration on the Mini-Mental Status Examination (MMSE) [138].

Table 1 Ferroptosis inhibitors

Lipid peroxidation inhibitors
• Vitamin E
• Deuterated polyunsaturated fatty acids
• Butylated hydroxytoluene
• Butylated hydroxyanisole
• Ferrostatins
• Liproxstatins
• Coenzyme Q10
• Idebenone
• Gliptins (vidagliptin, alogliptin, linagliptin)
Iron depleters
• Deferoxamine
• Cyclipirox
• Deferiprone
Lipoxygenase-induced lipid peroxidation inhibitors
• CDC (cinnamyl-3,4-dihydroxy-α-cyanocinnamate)
• Baicalein
• PD-146176
• AA-861
• Zileuton
System Xc- inhibitor blockers
• Cycloheximide
• 2-Mercaptoethanol
Blocker of GPX4 degradation
• Dopamine
Increased selenoproteins
• Selenium

Modified from Stockwell et al. [11]

Ideal Aspects of Chelators

There are a number of factors that potentially affect the efficacy and tolerability of iron chelators for AD and other neurodegenerative disorders.

The efficiency with which a chelator binds iron and its transmembrane transport properties appear to be major factors in efficacy [139]. A chelator for AD obviously needs to penetrate the blood–brain barrier. Chelators can remove iron from the site of accumulation directly, or transfer it to other molecules.

Use of nonselective chelators may affect the homeostasis of iron-dependent processes, such as depleting transferrin-bound iron in the plasma, leading to side effects [140, 141]. Moderate affinity chelators may be less likely than high-affinity chelators to remove metals from physiological processes [142]. Another strategy is utilizing site- or process-specific chelators,

such as pro-chelators, which have little affinity for metal ions until they undergo a chemical conversion in response to a specific stimulus [141]. Agents that target disease-specific pathophysiology, such as anti-ferroptotics, may also achieve the aim of modulating a disease process without affecting normal physiology. Given that iron may drive cell death by activating iron-sensing hypoxia-inducible factor prolyl hydroxylases, these could be a target of protection from ferroptosis via iron chelation [29].

Iron Chelators Currently Available

Iron chelators are currently used clinically for transfusion-dependent patients with iron overload and beta thalassemia major, sickle cell anemia, myelodysplasia, and aplastic anemia [143]. They are also used rarely in people with hemochromatosis who are unsuitable for phlebotomy due to severe cardiac involvement and unstable hemodynamics and in people with acute iron poisoning [143]. There are three iron chelators in widespread clinical use: deferoxamine, deferasirox, and deferiprone (Table 2) [143].

Deferoxamine is a siderophore obtained from *Streptomyces pilosus* which has been in clinical use since the 1970s [141, 144]. It is hydrophilic and large, with subsequent poor oral bioavailability, and poor blood–brain barrier permeability [144]. It also has a short half-life. Deferoxamine appears to act on extracellular iron [145]. It inhibits the iron redox cycle and modulates gene expression of hypoxia-inducing factor, iron regulatory protein-1, and APP, potentially blocking production of reactive oxygen species [146]. Deferoxamine binds in a 1:1 ratio with iron and is subsequently excreted in the urine and feces [147].

In APP/PS1 double transgenic mice, intranasal deferoxamine inhibited APP processing, induced activation of M2 microglia with amyloid-β phagocytic activity while inhibiting M1 proinflammatory microglia, and improved cognitive function [146, 148]. Deferoxamine also reduced amyloid [149] and tau [150] pathology in animal AD models.

In 1991, a placebo-controlled phase II clinical trial reported that 125 mg intramuscular deferoxamine dosed twice daily five times a week slowed cognitive decline in subjects with AD by 50% over a 24-month period [151]. This remains one of the few clinical trials for a potentially disease-modifying drug in AD that his shown cognitive benefit. At the time, the results were attributed to binding of brain aluminum [151]. The evidence for environmental exposure to aluminum playing a role in AD subsequently weakened [152], and the trial was never followed up to our knowledge. Deferoxamine's affinity for Fe^{3+}, however, is six times greater than for Al^{3+}, and iron is 1000-fold more abundant in the brain than aluminum, which suggests the positive results were due to iron chelation, rather than an effect on aluminum.

Deferasirox is an orally bioavailable high-affinity iron chelator which is capable of intracellular iron chelation. In rats, deferasirox prevented age-related accumulation of iron, reduced ferritin and transferrin receptor expression, and reversed altered amyloid-β metabolism [153]. Blood–brain barrier passage is limited, but improves when conjugated with lactoferrin [154]. Deferasirox binds at a 2:1 ratio to iron and is excreted in the feces [147]. Lactoferrin-deferasirox conjugates attenuated learning deficits induced by amyloid injection in a rat model of AD [154].

Deferiprone is an orally bioavailable siderophore with moderate iron-binding affinity [142, 144], which has been in clinical use since the 1980s [141]. It readily crosses the blood–brain barrier and chelates intracellular iron [145]. It is less aggressive than deferoxamine, which readily depletes the body of iron. Deferiprone penetrates cellular membranes, forms a complex with iron, exits cells, and can redistribute iron to transferrin for reuse [155, 156]. It binds iron with a 3:1 chelator/iron ratio and is primarily excreted via the kidneys [147].

Deferiprone is neuroprotective in neuronal culture models of amyloid-β toxicity [157, 158], protecting against hydrogen peroxide and Aβ1-40-induced neuronal death [158]. It attenuates amyloid burden and tau phosphorylation in a rabbit model of AD [159].

Clinical trials of deferiprone have taken place in a number of neurodegenerative disorders. A pilot study in Friedreich's ataxia, followed by a 6-month randomized controlled trial, showed that deferiprone can safely reverse pathological brain iron accumulation [155, 160]. A 12-month trial in neurodegeneration with brain accumulation followed, demonstrating that deferiprone was well tolerated over longer time frames [161]. FAIR-PARK 1, a phase II trial in Parkinson's disease, also showed that deferiprone was well-tolerated and did not lead to iron depletion [67]. Motor symptoms improved and R2* MRI showed a reduction in iron deposition in the substantia nigra [67]. FAIR-PARK 2, a phase III trial of deferiprone in Parkinson's disease, is nearing completion, with results expected in mid-2020.

A clinical of deferiprone in Alzheimer's disease is currently underway, the Deferiprone to Delay Dementia (3D Study; ClincalTrials.gov Identifier NCT03234686). This is a phase II randomized controlled study investigating the safety and efficacy of deferiprone in subjects with prodromal and mild

Table 2 Iron chelators in current clinical use

Agent	Oral bioavailability	Blood–brain barrier passage
Deferoxamine	No	Poor
Deferasirox	Yes	Limited
Deferiprone	Yes	Good

AD. The primary outcome is performance on a neuropsychological test battery. Secondary outcomes include brain iron levels as measured by MRI (T2*, QSM).

Clioquinol is an 8-hydroxyquinoline analogue. It is a copper/zinc ionophore and a moderate iron chelator [162]. It was withdrawn from clinical use due to a purported association with subacute myelo-optico-neuropathy, though whether an association exists is not clear [163]. Complications with large-scale manufacturing prevented further developments [162]. Clioquinol dissociates metals from binding sites in Aβ, decreases iron-associated Aβ42 aggregation [164], and stimulates amyloid degradation pathways via metal-dependent signalling. In a placebo-controlled phase II trial of 32 patients, clioquinol prevented cognitive deterioration and lowered plasma Aβ-42 levels [165].

Iron Chelators Under Development with Potential in Alzheimer's Disease

A number of compounds with iron-chelating activity have shown potential in *in vivo* AD models. There are also numerous novel compounds which have recently been developed (Table 3), some of which are described below.

Monoamine oxidase B leads to an increase in hydrogen peroxide and free radicals. A series of compounds combining MAO inhibition with iron chelation activity have been developed [166–168]. One of these, M30, is an orally bioavailable iron chelator which crosses the blood–brain barrier has shown promise in cell line and animal models. It combines monoamine oxidase A and B inhibitory activities with the antioxidant chelator moiety of VK28, an 8-hydroxyquinoline derivative [169]. M30 reduced APP expression and Aβ generation *in vitro* and reduced amyloid-β plaques in aged mice [169]. In APP/PS1 mice, it attenuated cognitive impairments, reduced cerebral iron accumulation, decreased cerebral APP levels, and reduced amyloid-β and tau levels [170]. This drug has not yet been tested in humans with AD to our knowledge.

There are several other iron chelators with *in vitro* evidence in support of a potential benefit in AD. A novel class of 2-amido-3-hydroxypyridin-4-one iron chelators shows neuroprotective properties in cell cultures against β-amyloid-induced toxicity [171]. Hydroxylated chalcones have recently been designed as dual-function inhibitors, with action against amyloid-β peptide aggregation and ferroptosis [172]. These have been shown in cell lines to provide protection against Aβ1-42 aggregation-induced toxicity and against ferroptosis [172]. HLA20A is a selective acetylcholinesterase inhibitor with site-activated chelating activity. It is activated following inhibition of acetylcholinesterase to liberate an active chelator, HLA20, which has neuroprotective activities. It has been shown to lower APP expression and amyloid-β generation and to reduce iron-induced aggregation [173].

A number of other dual-function therapeutics have been developed with iron-chelating and acetylcholinesterase-inhibiting properties. Tacrine-(hydroxybenzoyl-pyridone) hybrids, combining acetylcholineserase inhibition and iron-chelating capacity have been developed [174]. There are also tacrine-deferiprone hybrids [175]. Novel dihydropyrimidinone-derived selenoesters have been synthesized with anti-oxidant activity via lipid peroxidation inhibition and iron chelation activity as well as acetylcholinesterase inhibition [176]. Quinazoline and pyrido(3,2-d)pyrimidine, and 3-hydroxy-4-pyridinone)-benzorufan-based compounds have also been synthesized, with dual cholinesterase

Table 3 Some iron chelators and related compounds under development with potential in AD

Agent	Mechanism of action
M30	MAO-I + IC
2-Amido-3-hydroxypyridin-4-one compounds	IC
Hydroxylated chalcones	Anti-Aβ aggregation + anti-ferroptotic
HLA20A	ACh-I + IC
Tacrine-(hydroxybenzoyl-pyridone) hybrids	ACh-I + IC
Tacrine-deferiprone	ACh-I + IC
Dihydropyrimidinone-derived selenoesters	ACh-I + IC + anti-oxidant
Quinazoline-pyrido-benzorufan-based compounds	ACh-I + IC
3,4-HP-based compounds	Anti-Aβ aggregation + ACh-I + IC
Benzothiazone-based compounds	Anti-Aβ aggregation + ACh-I + IC
Coumarin-quinoline hybrids	ACh-I + IC
1-Phenyl-3-hydroxyl-4-pyridinone derivatives	Anti-Aβ aggregation + IC + anti-oxidant
Cu^{II}(atsm)	Anti-ferroptotic
PBPT	ACh-I + CI

MAO-I = monoamine oxidase inhibitor; IC = iron chelator; ACh-I = acetylcholinesterase inhibitor

inhibition and iron-chelating properties [177, 178]. Similarly, multifunctional iron chelators with anti-Aβ-aggregating and acetylcholinesterase-inhibiting activity have been developed from 3-hydroxyl-4-pyridinone (3,4-HP) and benzothiazole molecular moieties [179].

Circumin has been proposed as an AD therapeutic in light of its iron-binding capability [180]. A number of derivatives have been developed, including coumarin-quinoline hybrids with acetylcholinesterase and iron chelation activity [181] and hybrids of hydroxypyridinone and coumarin, which ameliorated cognitive dysfunction in scopolamine-induced AD mice [182].

Novel 1-phenyl-3-hydroxyl-4-pyridinone derivatives with iron-binding capabilities have been synthesized as potential AD therapeutics by incorporating the 3-hydroxy-4-pyridinone moiety from deferiprone into the scaffold of H3 receptor antagonists. Some of these combine iron chelating, amyloid-β aggregation inhibition, metal chelating, and free radical scavenging actions [183].

Chelators based on Schiff bases, particularly hydrazones and thiosemicarbazones, also have potential in neurodegenerative diseases based on their ability to suppress oxidative stress caused by redox-active metals and metal-induced aggregation of amyloid beta [139]. Cholyl hydrazones have been shown to can reduce amyloid-β toxicity and oxidative stress in cell lines [139]. Diacetyl-bis(4-methyl-3-thiosemicarbazonato)copper^{II} (Cu^{II}(atsm)) is a bisthiosemicarbazone that protects against lipid peroxidation and ferroptotic lethality *in vitro* [184]. Cu^{II}(atsm) is orally bioavailable and crosses the blood–brain barrier [184]. Phase I trials in Parkinson's and motor neuron diseases have recently been completed with promising results [185, 186]. Cu^{II}GTSM lowered Aβ levels and phosphorylated tau levels in cell culture and APP/PS1 transgenic mice [187].

Multifunctional hybrids based on hydrazones and thiosemicarbazones are in development. This includes novel adamantine-based semicarbazones and hydrazones [188] and hybrid molecules containing a metal binding unit, a thiosemicarbazone, and acetylcholinesterase inhibitor such as PBPT (pyridoxal 4-*N*-(1-benzylpiperidin-4-yl)thiosemicarbazone) [189].

Very few iron chelators have made it to clinical trials in humans in spite of the development of the above and other compounds. A search of clinicaltrials.gov using the terms "iron" and "Alzheimer's" on 24 June 2020 only yielded the 3D study discussed above.

Conclusion

An extensive body of data in support of a role of iron in the pathophysiology of Alzheimer's disease is emerging. This work ties in with the pathology of amyloid-β and tau at many levels. Cell line and animal studies of iron chelators for AD show encouraging results. In spite of this, there has been very little work on iron-lowering strategies in humans with AD, likely due to an overemphasis on amyloid-lowering strategies which have been overwhelmingly disappointing to date. Given the growing number of iron-chelating compounds with potential disease-modifying efficacy, and the availability of MRI and CSF biomarkers of iron load, there is considerable scope to explore this therapeutic class in AD.

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Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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