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REVIEW ARTICLE

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Iron and oxidizing species in oxidative stress and Alzheimer's disease

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Abstract

Iron species can participate in the Fenton or Fenton-like reaction to generate oxidizing species that can cause oxidative damages to biomolecules and induce oxidative stress in the body. Furthermore, iron accumulation and oxidative stress have been shown to associate with the pathological progression of neurodegenerative disorders, including Alzheimer's disease (AD) and Parkinson's disease (PD). In this review, the role of iron species in generating the most deleterious free radical species (ie, hydroxyl radical) and effects of this species in causing oxidative stress in vivo are described. The implications of oxidative stress and the recently recognized cell death pathway (ie, ferroptosis) to AD are addressed. Strategies to combat this neurodegenerative disease, such as iron chelation and antioxidant therapies, and future research directions on this aspect are also discussed.

KEYWORDS

Alzheimer's disease, Fenton/Fenton-like reaction, hydroxyl radical, iron species, oxidative stress

1 | INTRODUCTION

Iron is an essential element of the body. However, its iron(II) species (ie, iron(II) ions or iron(II)-L complex [L, a coordinated ligand]), can participate in Fenton or Fenton-like reactions to react with H_2O_2 and generate one of the reactive oxygen species (ROS), hydroxyl radical ($^{\bullet}OH$).[1-3] Because the $^{\bullet}OH$, H^+/H_2O couple has a high electrode potential of +2.31 V (at pH7.0),[4] hydroxyl radical can react with many biomolecules by hydrogen abstraction and hydroxyl addition at diffusion-controlled rates (bimolecular rate constant $k \approx (0.5\text{-}2) \times 10^{10}\ M^{-1}\ s^{-1}$).[4,5] It is therefore the most deleterious ROS and can cause various types of oxidative damages to DNA, proteins, and cells.

In vivo, when the antioxidant defenses from enzymes and physiological antioxidants are overwhelmed with the overproduction of ROS for keeping the pro-oxidation-antioxidation balance, oxidative damage of biomolecules may occur and this condition is called *oxidative stress*. Studies have shown convincing evidence that neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), are associated with oxidative stress in the affected region of the brain.[1,6-9]

Among the transition metals associated with AD pathology, including iron, copper, and zinc, iron is the most abundant in the healthy brain for normal brain function. On the other hand, iron accumulation and oxidative stress are shown as early events in AD, and the presence of elevated levels of redox-active iron has been suggested as a potential event in triggering amyloid-β (Aβ) aggregation and oxidative damage of the brain.[10] Furthermore, ferroptosis, a recently recognized iron-dependent programmed cell death, is not only caused by the accumulation of lipid-based ROS, but also suggested as the main driver of neurological cell death in diseases such as AD and PD.[11-15] Therefore, a better understanding of the roles of iron and the oxidizing species (generated by iron) in oxidative stress and AD is essential for developing pharmaceutical interventions to

treat neurodegenerative diseases. In this review, we examine the role of iron species in generating the most oxidatively deleterious ROS (ie, •OH) and describe the oxidative damages caused by this free radical and its consequence of inducing oxidative stress. We also discuss the association of oxidative stress with AD and the potential therapeutic strategy for this disease.

2 | IRON-INDUCED GENERATION OF OXIDIZING SPECIES

2.1 | Generation of the hydroxyl radical from Fenton/Fenton-like reactions

In aqueous solutions, the hydroxyl radical can be generated by the Fenton reaction (see Reaction 1), which was named after the discoverer of the catalytic oxidation of tartaric acid by H_2O_2 in the presence of iron(II) aqueousions.[16,17] It can also be produced from reactions of iron(II) complexes with a ligand (L) and other transition metal complexes (M^n-L; M: other transition metals, eg, copper; n: oxidation state) with H_2O_2, called *Fenton-like reactions* (see Reactions 2 and 3, respectively).[3]

$$Fe(II) + H_2O_2 \rightarrow Fe(III) + {}^{\cdot}OH + OH^- \quad (1)$$

$$Fe(II) - L + H_2O_2 \rightarrow Fe(III) - L + {}^{\cdot}OH + OH^- \quad (2)$$

$$M^n - L + H_2O_2 \rightarrow M^{n+1} - L + {}^{\cdot}OH + OH^- \quad (3)$$

In a lipid environment, the Fenton-like reactions of iron(II) species or other transition metals with lipid peroxide (ROOH), similar to Reactions 1-3, can also take place to produce lipid alkoxy radicals (RO•; see Reactions 4-6.

$$Fe(II) + ROOH \rightarrow Fe(III) + RO^{\cdot} + OH^- \quad (4)$$

$$Fe(II) - L + ROOH \rightarrow Fe(III) - L + RO^{\cdot} + OH^- \quad (5)$$

$$M^n - L + ROOH \rightarrow M^{n+1} - L + RO^{\cdot} + OH^-. \quad (6)$$

It has been proposed that in addition to hydroxyl radical, an iron(IV) species may also be generated from the Fenton or Fenton-like reactions.[2,3] However, the formation of this species from a Fenton reaction was confirmed recently only in aqueous solution[18] and its biological relevance has not been proven. Furthermore, we have recently demonstrated convincing nuclear magnetic resonance spectroscopy-evidence that the oxidizing species generated from the Fenton-like reaction of iron(II)-citrate with hydrogen peroxide is hydroxyl radical rather than the iron(IV) species.[19] Therefore, in this review regarding the oxidizing species generated from Fenton/Fenton-like reactions, we focus on hydroxyl radical rather than the iron(IV) species.

2.2 | Iron species engaged in Fenton-like reactions in vivo

The participation of iron species in Fenton and Fenton-like reactions leads to generation of oxidizing species that can induce oxidative damage to biomolecules. Therefore, iron species, especially their iron(II) forms, have potential toxicity in causing oxidative stress and pathological processes.[1,2,6,7,20-24] In vivo iron in the labile (cellular chelatable or redox-active) iron pool is in the iron(II) form bound to proteins or physiological ligands, such as citrate.[2] The concentrations of redox-active iron and citrate in the blood plasma are estimated to be 15-50 μmol/L[2,25] and 0.1 mol/L,[26] respectively. Iron-citrate complexes are found in the blood serum of patients under pathological conditions of iron overload and also in synovial fluid from patients with rheumatoid arthritis.[26-29] In vivo H_2O_2 can be produced by several enzymes, including xanthine oxidases and superoxide dismutase, and the concentration of plasma H_2O_2 is in the range of 1-5 μmol/L.[30] Thus, in vivo the two reactants of the Fenton-like reaction, the iron(II)-citrate complex and H_2O_2, are readily available. The Fenton-like reaction of iron(II)-citrate with H_2O_2 has been suggested as one of the mechanisms of the labile iron pool that may induce oxidative stress and cause pathological processes in the body.[2,22,24]

Furthermore, lysosomes also contain a redox-active iron pool derived from macromolecules and cellular organelles rich in iron, such as ferritin and mitochondria.[2,31] One of the possible sources of intracellular redox-active iron is degradation of ferritin inside lysosomes during the process of autophagy.[32] The hydrogen peroxide diffused into lysosomes may react with the iron species through the Fenton and Fenton-like reactions, which results in generation of hydroxyl radicals.[2]

3 | HYDROXYL RADICAL CAUSED OXIDATIVE DAMAGE TO BIOMOLECULES

The *ROS* is a general term for several radical and non-radical species, including singlet oxygen, superoxide radical, hydrogen peroxide, and hydroxyl radical.[20] Singlet oxygen is not found in animals[20] and thus it is not directly relevant to neurodegenerative diseases. Superoxide radical is a mild reductant and hydrogen peroxide is also a relatively stable species.[2,20] Therefore, we focus on the hydroxyl radical in this article.

We have noticed that because hydroxyl radical can react with many molecules at diffusion-controlled rates, the attacks by hydroxyl radicals have been suggested to be non-selective and less damaging at the crucial sites of biomolecules. However, it should be pointed out that these non-selective attacks can rapidly generate other radical species that can subsequently react with oxygen molecules to form peroxyl radicals, and these radicals can selectively induce oxidative damage to biomolecules, such as peroxidation of proteins.[4] Furthermore, a recent study has demonstrated that hydroxyl radicals produced from Fenton reaction can cause localized attacks in the nuclear DNA.[33] Therefore, the deleterious power of hydroxyl radical in causing oxidative damages to biomolecules should not be overlooked.

3.1 | Oxidative damage of DNA and RNA caused by hydroxyl radical

Hydroxyl radical can cause oxidative damage to all components of DNA, including all bases and the deoxyribose backbone.[2] This

damage can result in permanent modifications of the DNA and thus further lead to mutagenesis, carcinogenesis, and aging.[34] It has been demonstrated that the damage caused by hydroxyl radical from the Fenton reaction is localized in the nuclear DNA. These site-specific attacks to DNA are mainly induced by additions of hydroxyl radical to the double bond at C4 of the adenosine in nuclear DNA.[33]

The oxidation of DNA and RNA caused by hydroxyl radical can be detected by using the 8-hydroxy-2-deoxyguanosine (8OHdG) and 8-hydroxyguanosine (8OHG) as markers, respectively.[35] The increased level of 8OHG has been found in the neuronal perikaryal cytoplasm and this is relevant to neurofibrillary tangles, a hallmark lesion of AD.[36]

3.2 | Oxidative damage of lipids and proteins caused by hydroxyl radical

Hydroxyl radical can react with biomolecules by hydrogen abstraction and hydroxyl addition to form other radical species that can subsequently react with oxygen molecules to form peroxyl radicals. These peroxyl radicals can cause lipid peroxidation of membranes and protein peroxidation.[4] Lipid peroxidation can be demonstrated by altered phospholipid composition and several markers, such as thiobarbituric acid reactive substances, malondialdehydes, 4-hydroxy-2-transnonenal, and isoprostane, which indicates altered membrane integrity.[35]

Oxidative modifications of metabolic proteins, including creatine kinase BB, cytochrome c oxidase, and ketoglutarate dehydrogenase complex, have been evidenced by elevated levels of protein carbonyl and nitration of tyrosine residues, and these oxidative modifications can cause impaired metabolic activity of the proteins.[35,37] These peroxidation and oxidative modifications of proteins have been elevated in AD compared with control cases.[37]

4 | IRON AND OXIDIZING SPECIES IN OXIDATIVE STRESS AND AD

4.1 | Sources of redox-active iron species in AD

Because iron accumulation and oxidative stress have been shown as early events in AD, the presence of elevated levels of redox-active iron could be a key factor in causing Aβ aggregation and oxidative damage in the disease.[10] However, the precise source of redox-active iron integrated into amyloid plaque cores is not known. Multiple sources of iron may be engaged in the amyloid-iron interaction in AD, such as ferritin, transferrin, and the labile iron pool.[10]

Surprisingly, although mitochondria consist of various iron-containing functional biomolecules, such as heme, cytochrome, and aconitase, little DNA oxidation marker (8OHdG) is accumulated in mitochondria.[36] On the other hand, since lysosomes possess macromolecules and cellular organelles rich in iron, lysosomes could be a potential metabolic source of iron that can cause oxidative damage to cells.[2] The acidic (pH4-5) and reducing environment inside lysosomes ensures that the iron species degraded by autophagy are in their iron(II) forms, which are able to directly react with H_2O_2 through the Fenton and Fenton-like reactions (see Reactions 1 and 2). Furthermore, in lysosomes, active catalase for converting H_2O_2 to harmless H_2O and O_2 is absent. Therefore, the H_2O_2 diffused into the lysosomes can readily react with the iron(II) species there by the Fenton/Fenton-like reactions to generate hydroxyl radicals.[2] Hydroxyl radicals can cause lipid peroxidation of membranes, resulting in subsequent release of redox-active iron into the cytosol.[38] This leads to increased concentration of labile iron pool that may cause cell damage and result in apoptosis or necrosis relevant to the neurodegenerative process.[39]

4.2 | Recently recognized cell death pathway associated with iron, oxidizing species, and AD

Ferroptosis is a recently recognized form of iron-dependent programmed cell death that is caused by the accumulation of lipid-based ROS.[11,13] For decades before ferroptosis was recognized, brain cell death has been attributed to apoptosis or necrosis.[40] However, ferroptosis cannot be prevented by well-known small-molecule inhibitors of apoptosis, necrosis, or autophagy.[31] With the accumulation of evidences correlating elevated iron levels and increased lipid peroxidation in the brains of AD patients to the pathological processes, ferroptosis has now been suggested as the main driver of neurological cell death in AD.[11,12,14,15]

Although the exact role of iron in ferroptosis remains elusive, one possible underlying mechanism is the Fenton and Fenton-like reactions of iron species with lipid peroxides to produce oxidative radical species (see Reactions 4-6).[41] This hypothesis is supported by the evidence that ferroptosis can be prevented by lipophilic antioxidants, such as vitamin E, and by iron chelators, including deferoxamine.[31]

Ferroptotic death is often correlated to the disruption of iron homeostasis, resulting in an increased level of redox-active iron, in particular the iron(II) species.[11] Interestingly, study has shown recently that deleting mitochondria from cells does not prevent ferroptosis, indicating that ferroptotic death does not need mitochondria.[11,42]

5 | STRATEGIES TO COMBAT AD

5.1 | Iron chelation for treatment of AD

The presence of elevated levels of redox-active iron has been suggested as a potential event causing Aβ aggregation and oxidative damage of the brain.[10] Thus, therapeutic interventions with iron chelators that target iron metabolism have been developed. For instance, the iron chelator deferiprone can cross the blood-brain barrier and reduce the abnormally high concentration of cerebral iron in the brain.[43] However, to date, treatments of neurodegenerative diseases by iron-chelating agents have not demonstrated compelling clinical effect.[43] The failures may be due to lack of specificity leading to depletion of iron stores and other essential metals required for maintaining neuronal health.[10]

5.2 | Antioxidants for treatment of AD

Targeted antioxidant is an emerging strategy to combat the deleterious effects of ROS, in which small molecules that preferentially scavenge ROS at specific intracellular sites are designed or identified.[31] For instance, a conjugate of the nitroxide molecule 2,2,6,6-tetramethyl-piperidine-1-oxyl (Tempo) and a peptide mitochondria-targeting sequence (Leu-d-Phe-Pro-Val-Orn) called *XJB-5-131* was synthesized to reduce the oxidative damage caused by ROS in mitochondria.[44] XJB-5-131 has shown remarkably beneficial effects in a mouse model of neurodegenerative disease (Huntington's disease), such as reducing oxidative damage to mitochondrial DNA, enhancing neuronal survival, and improving mitochondrial function.[45]

The nitroxide Tempo is capable of permeating cell membranes and crossing the blood-brain barrier. In vivo studies using animal models have shown that nitroxides have promising potential as therapeutic antioxidants.[46,47] However, the underlying mechanism of nitroxides' antioxidation is not well understood and there are controversial findings from in vitro studies.[48,49] Recently, we studied the effect of nitroxide Tempo on the physiologically important Fenton-like reaction of iron(II)-citrate with hydrogen peroxide. We demonstrated that Tempo can effectively inhibit the production of hydroxyl radical by oxidizing the iron(II)-citrate to iron(III)-citrate and hence blocking the Fenton-like reaction (see Reaction 2).[50]

An effective antioxidant may reduce the oxidative damage caused by hydroxyl radicals from Fenton or Fenton-like reactions in the following ways: (a) the proactive approach—blocking or inhibiting the reaction that produces ROS; or (b) the reactive approach—scavenging ROS or converting them into harmless species. The proactive approach by blocking or inhibiting the reaction would be more effective than that by scavenging the radical, since hydroxyl radical can react with many biomolecules at diffusion-controlled rates (see Section 1). To scavenge hydroxyl radical, the antioxidant must react with it before the radical reacting with biomolecules, and this requires not only the presence of antioxidant at the vicinity of the radical, but also a higher reactivity and concentration than those of the biomolecules.

On the basis of our in vitro study,[50] it is possible that XJB-5-131 may reduce the oxidative damage to mitochondrial DNA by oxidizing the iron(II) species and hence blocking the Fenton-like reaction (see Reaction 2). This assumption, however, does not rule out the possibility that XJB-5-131 may also scavenge hydroxyl radicals by spin-trapping pathway, as long as XJB-5-131 can appear at the right place and time, and with a high enough reactivity and concentration.

For inhibiting the ferroptosis, several potential antioxidants have been developed or discovered. For instance, a small molecule, ferrostatin-1, was synthesized as an inhibitor of ferroptosis and it can also prevent glutamate toxicity in rat hippocampal slice cultures.[31,51] In addition, vitamin E has been suggested as an inhibitor of lipoxygenase and subsequently inhibits ferroptosis.[11] CoQ10, an endogenously produced lipid-soluble antioxidant, has been shown to reduce the oxidative damage of proteins, lipids, and DNA caused by ROS.[52] The potential role CoQ10 in reducing ferroptotic death deserves further investigation. However, exogenously supplemented vitamin E and CoQ10 tend to be retained in cell membranes due to their lipophilic nature. Thus, it is difficult for these supplemented compounds to achieve the intracellular concentrations of pharmacological significance.[53]

6 | CONCLUSIONS

Iron(II) species can participate in the Fenton and Fenton-like reactions to react with H_2O_2 and generate one of the most deleterious ROS, hydroxyl radical. Hydroxyl radical can instantly react with biomolecules and cause various types of oxidative damage to DNA, proteins, and cells. In vivo, the overproduction of ROS may overwhelm the physiological antioxidant defenses and lead to oxidative stress. As iron accumulation and oxidative stress have been shown to associate with the pathological progression of neurodegenerative diseases, including AD and PD, iron-chelation and antioxidant therapies have become strategies to combat these diseases. However, neither of these therapies has demonstrated compelling evidence of the clinical effect. Iron-chelation therapy may cause the depletion of iron stores required for maintaining neuronal function and health. Thus, it is essential to design the iron-chelating agent that targets only the specific iron species, especially the iron(II) complexes with physiological ligands in the labile iron pool. In regards to antioxidant therapy to reduce oxidative damage caused by the hydroxyl radical, blocking or inhibiting Fenton/Fenton-like reactions is a more effective approach than scavenging the extremely reactive hydroxyl radical. Due to the complexity of the redox system in vivo, a combination of a multifaceted approach, including iron-chelation and antioxidant, may be an attractive therapeutic strategy. Further investigations along this line are highly expected for the prevention and treatment of neurodegenerative diseases in future.

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CONFLICTS OF INTEREST

Nothing to disclose.

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