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Oxidative Stress Gated by Fenton and Haber Weiss Reactions and Its Association With Alzheimer's Disease

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Context: Involvement of reactive oxygen species (ROS) in a variety of physiological and pathological processes has attracted a growing interest. In fact, identification of this global signaling system has provided new insights into underlying pathophysiological mechanisms of various diseases such as Alzheimer's disease (AD). Understanding this information may lead to the development of novel therapeutic strategies.

Evidence Acquisitions: Limited efficacy of current medications for neurological disorders and dementias such as AD has led to considerable research interests in new drug development. Based on the modulatory effects of the Fenton reactions with transition metals such as iron, copper, zinc and aluminum on ROS and the effect of free radicals on neuroinflammatory and neurodegenerative processes, we hypothesized that pharmacological manipulation of the transition metals gated hydroxyl ion might be beneficial in treating neurological disorders such as AD.

Results: Catalytic activities of transition metals gated by the Fenton reactions are involved in the survival and pathological signaling pathways, neural plasticity, and neuroprotection. Furthermore, ROS and RNS have proved to exhibit overwhelming pathological effects leading to a variety of neurological disorders.

Conclusions: In the present investigation, an overview was made on regulatory role of the Fenton reaction gated catalytic activities of transition metals and some evidence regarding their mechanisms leading to Alzheimer's disease. Based on the neuroinflammatory and neurodegenerative effects of transition metals, drugs with antagonizing effects could be a promising therapeutic alternative for Alzheimer's disease.

Keywords: Fenton Haber Weiss Reactions; Reactive Oxygen Species; Metals; Alzheimer's disease

1. Context

The Fenton and Haber Weiss reaction plays a significant role in oxidative stress causing numerous degenerative diseases such as Alzheimer's disease (AD). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced by the reaction causing oxidative stress in AD. Iron, copper and aluminum promote the formation of free radicals such as Hydroxyl radicals causing damage to DNA, proteins, lipids and carbohydrates. Hydroxyl radicals produced by Fenton reaction, causes the A β 42 toxicity (1, 2) in AD. Hydroxyl radicals can be produced in the presence of Ferric ions and converts soluble human fibrinogen into an insoluble fibrin-like aggregate observed in neurodegenerative diseases such as AD (3). DNA bases can be modified by the Fenton gated oxidative stress and base substitutions G \rightarrow C (in the presence of Ferrous), G \rightarrow T and C \rightarrow T (Copper and Nickel) (4) by the reaction with ROS. Signal transduction molecules, such as extracellular signal-regulated kinase 1 and 2 (ERK1/2), c-Jun N-terminal kinase (JNK), phosphoinositide 3-kinase (PI3K), p38 and transcription factors such as

activator protein-1 (AP-1), and p53 are activated by ROS (4, 5). Hydroxyl radicals can damage DNA by p53 pathway and accelerate AD development. Mutation in tumor suppressor gene (TP53) is associated with AD pathogenesis (2, 6).

Oxidative stress is mainly produced by the Fenton reaction by removal of one electron from the molecular oxygen (O₂) results in the formation of superoxide (O₂⁻) which often produces other ROS species such as H₂O₂ and Peroxynitrite (ONOO⁻) and hydroxyl radicals (OH[•]) (7). However under normal conditions, O₂⁻ has been emerged as an important signaling molecule, which controls specific biochemical reactions and metabolic processes (8). The link between O₂⁻ production and H₂O₂ can involve a reduced flavin enzyme, which transfers an electron to activate molecular oxygen into superoxide which either released or enzymatically converted into H₂O₂ (9, 10) or modified by drugs such as statins (11).

One of the greatest challenges in the field of ROS-gated diseases is to bridge the knowledge gap between atomic

and cellular level, and more understanding of the Fenton reaction may help to bridge this gap. In 1890, Fenton used a solution of H_2O_2 and Iron to oxidized contaminants of waste water. When transient metals such as iron react with hydrogen peroxide (H_2O_2), it produces Ferric (Fe^{+++}), hydroxyl radical ($\text{OH}\cdot$) and hydroxyl ion (OH^-). Hydroxyl ion (OH^-) reacts with H_2O_2 again to produce superoxide (O_2^-) and hydroxyl ion (OH^-).

Reactive oxygen species (ROS) are produced as the by-product of the electron transport chain (ETC) in mitochondria and are responsible for lipid peroxidation, protein oxidation, DNA damage and advanced glycation end-products (AGEs) formation via effects of ROS on cellular signaling pathways.

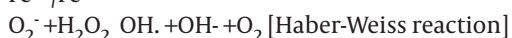
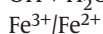
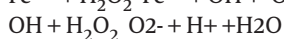
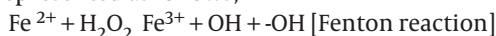
2. Evidence Acquisitions

2.1. Oxidative Stress and AD

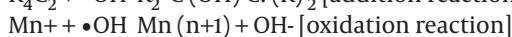
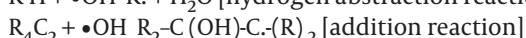
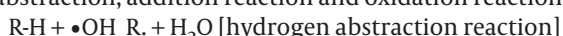
Our early work on the effect of herbs on ROS (12-14) genes mutation in AD (15), effect of metals on gene modification in psychiatric disorders (16) and effect of ROS on neurological disorders (17) indicate underlying importance of the Fenton reaction. We searched any evidence (18-21) responsible for AD pathogenesis.

2.2. Fenton and Haber-Weiss Chemistry

Since brain is the most aerobically active organ in the body, ROS is mostly produced in the brain. Iron (Fe), copper (Cu), zinc (Zn) and aluminum (Al), due to their multiple valence states can react with the molecular oxygen and produce ROS and RNS. The Fenton and Haber-Weiss reaction has a significant role in ROS production and AD pathogenesis. The Fenton reaction is defined as the reaction of ferrous iron (Fe^{2+}) and hydrogen peroxide (H_2O_2). In this reaction, ferric iron (Fe^{3+}) and hydroxyl radical ($\text{OH}\cdot$) are produced. Then hydroxyl radical ($\text{OH}\cdot$) reacts with H_2O_2 and superoxide (O_2^-) is produced. Then superoxide reacts again with H_2O_2 , hydroxyl radical ($\text{OH}\cdot$) and hydroxyl anion ($-\text{OH}$) are formed; this part of reaction is known as the "Haber-Weiss Reaction". Superoxide (O_2^-) reduces to Fe^{3+} rather than H_2O_2 . The overall reaction is represented as follows;



Several metals such as Fe, Cu, Zn and Al have oxygen-transferring properties for the catalytic power to generate highly reactive $\cdot\text{OH}$ by the Fenton reaction. $\cdot\text{OH}$ is the most powerful oxidant for the oxidative stress in AD. $\cdot\text{OH}$ is mainly involved in three types of reaction as hydrogen abstraction, addition reaction and oxidation reaction.



2.3. Metals Causing Oxidative Stress in AD

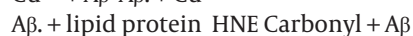
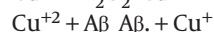
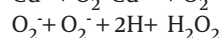
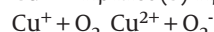
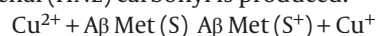
2.3.1. Iron in AD

Iron has a pivotal role in oxidative stress by the formation of hydroxyl radical through Fenton reaction in AD pathogenesis. Fe^{2+} is oxidized to Fe^{3+} by oxygen molecule (O_2), O_2^- is produced. O_2^- reacts with hydrogen ion (H^+) and H_2O_2 is produced. Then H_2O_2 reacts with Fe^{2+} and $\cdot\text{OH}$ is produced by the Fenton reaction. Then $\cdot\text{OH}$ is produced again by the reaction of hydrogen peroxide in the presence of $\text{Fe}^{3+}/\text{Fe}^{2+}$ via the Haber-Weiss reaction.

Lovell et al. in 1998 found that Fe concentration in AD plaques ($\sim 1 \text{ mmol L}^{-1}$) is more than normal brain tissue ($\sim 350 \mu\text{mol L}^{-1}$) (22). In vitro studies also showed that Fe induces A β aggregation (23) and tau phosphorylation (24).

2.3.2. Copper in AD

Copper (Cu) is also an important catalyst for production of ROS. Cu can bind with A β peptide, this Cu-A β peptide can produce H_2O_2 through reduction of Cu^{2+} to Cu^+ and subsequently hydroxyl radical ($\cdot\text{OH}$) is produced, which increases oxidative stress and causes neuronal death (25). A β is converted to A β ; as a result A β exhibits the greatest activity of A β aggregation in AD pathogenesis (26). A β can also cause lipid protein oxidation and 4-hydroxy-2-nonenal (HNE) carbonyl is produced.



Activity of cytochrome C-oxidase (27), copper/zinc peroxidase (28) and ceruloplasmin (29) are diminished by free radicals. Lower level of ceruloplasmin may increase lipid peroxidation (30). Reduction of Cu^{2+} to Cu^+ by A β enhances oxidative stress by the production of $\cdot\text{OH}$ and further neuronal damage in AD (31). Interaction of Cu with tau peptide may also induce neurofibrillary tangles (32). In vitro studies revealed that Cu^{2+} and Zn^{2+} promote neurotoxicity by the generation of H_2O_2 (33, 34). Literature indicated that A β - Cu^{2+} stimulates ROS production (33, 35) by the Fenton and Haber-Weiss reaction, causing oxidative stress and AD.

2.3.3. Zinc in AD

Zn binds to A β . Zn-A β complex is transiently stable prior to aggregation (36, 37) and contains less fibril (38). When Zn binds to A β -peptide via histidine residues, then Zn-A β complex changes their conformation and copper cannot bind to A β . In this way, Zn can prevent Cu-A β induced H_2O_2 and free radicals. The possible mechanism might be due to its competition with Cu or Fe. Low concentration of Zn protects A β toxicity, but excessive Zn causes

neuronal death by the oxidation independently or synergistically. Higher concentration of Zn^{2+} binds to A β and precipitates at pH 6-8 (39).

2.3.4. Aluminum in AD

Aluminum (Al) can accelerate oxidative stress in vivo and in vitro (40). Aluminum superoxide semireduced radical ions (AlO_2^{2+}) are produced by the reaction of Al^{3+} with superoxide (O_2^-). AlO_2^{2+} then reduces Fe^{3+} to Fe^{2+} and promotes the oxidative stress through the Fenton and Haber-Weiss reaction (41-43).

2.4. DNA Damage

Hydroxyl radical ($\bullet OH$) plays a critical role in nucleic acids damage (44). It is produced by the Fenton reaction. $\bullet OH$ can react with DNA by either hydrogen abstraction or addition reaction. When hydroxyl radical reacts in hydrogen abstraction, leading to disruption of DNA strand and when hydroxyl radical takes part in addition reaction, then deoxyguanosine is converted to 8-hydroxy deoxyguanosine (8-OHdG) (45).

$OH + DNA \rightarrow DNA \text{ strand breaks [hydrogen abstraction]}$

5-hydroxymethyluracil and hydroxyadenine are produced by the reaction of ROS with thymine and adenine respectively (46). In oxidative deamination, NH_2 group is substituted by $-OH$ group of Nucleic acid. As a result, adenine cytosine and guanine are transformed to hypoxanthine, uracil and xanthine, respectively. Therefore, deamination of DNA can cause in GC \rightarrow AT transition in oxidative stress (47, 48).

Purine and pyrimidine bases can produce 20 different oxidative products of DNA with the interaction of $\bullet OH$ (49). 8-hydroxyguanine, 8-Hydroxyguanosine (8OHG), 8-hydroxyadenine, thymine glycol, Fapy-guanine, 5-hydroxyuracil and Fapy-adenine are major products of DNA oxidation by the reaction of ROS and RNS (50) found in parietal, temporal, occipital, frontal lobe, superior temporal gyrus, hippocampus of brains of patients with AD (51). It is indicated that DNA damage is performed by the Fenton reaction in AD pathogenesis.

2.4. Lipid Peroxidation

Due to the presence of double bonds, polyunsaturated fatty acid, is highly reactive towards free radicals mainly hydroxyl radical. Two reaction mechanisms are proposed for lipid peroxidation as hydroxyl radical dependent and hydroxyl independent. Fe^{2+} acts as a positive catalyst for the production of hydroxyl radical dependent lipid peroxidation.

Hydroxyl radical dependent mechanism:

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \bullet OH + -OH$ [The Fenton and Haber-Weiss reaction]

Hydroxyl independent mechanism:

$Fe^{2+} + O_2 \rightarrow [Fe^{2+}-O_2] \leftrightarrow [Fe^{3+}-O_2^-] \rightarrow Fe^{3+} + O_2^-$

$Fe^{3+} + O_2^- \rightarrow O_2 + Fe^{2+}$

$Fe^{2+} + H_2O_2 \rightarrow Fe^{2+}O + H_2O$

$Fe^{2+} + Fe^{2+}-O_2 \rightarrow Fe^{2+}-O_2^- + Fe^{2+} \rightarrow 2 Fe^{2+}-O_2$

Lipid (LH) peroxidation is performed by the following three steps (52);

a) Initiation:

$LH + \bullet OH \rightarrow L\bullet + H_2O$

b) Propagation:

$L\bullet + O_2 \rightarrow LOO\bullet$

$LOO\bullet + LH \rightarrow L\bullet + LOOH$

$LOOH \rightarrow LO\bullet + -OH$

c) Termination:

$L\bullet + L\bullet \rightarrow L-L$

$L\bullet + LOO\bullet \rightarrow LOOL$

$LOO\bullet + LOO\bullet \rightarrow LOOL + O_2$

Transition metals such as copper and iron can act as a positive catalyst in initiation and propagation steps of lipid peroxidation.

$Cu^{+} + LOOH \rightarrow LO\bullet + -OH + Cu^{2+}$

$Cu^{2+} + LOOH \rightarrow LOO\bullet + Cu^{+}$

$2LOOH \rightarrow LO\bullet + LOO\bullet + H_2O$

Polyunsaturated fatty acids (PUFAs) are mainly targeted by these radicals due to the presence of double bonds and produce polyunsaturated fatty acid-free radicals ($LO\bullet$, $LOO\bullet$). Malondialdehyde (MDA) is then produced by the cyclization reaction of end peroxides and peroxy radicals ($ROO\bullet$) (53, 54). 4-hydroxy-2-nonenal (HNE) and malondialdehyde (MDA) as lipid peroxidation products are formed in mitochondria (Figure 1) (55).

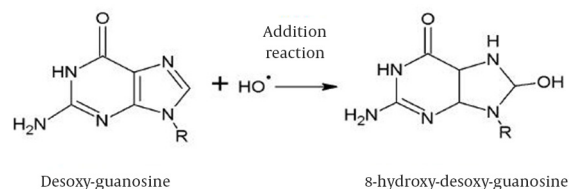


Figure 1. $OH + DNA \rightarrow DNA \text{ Strand Breaks [Hydrogen Abstraction]}$

2.5. Protein Oxidation

Free amino acids and proteins are oxidized to corresponding aldehyde and carboxylic acid by hydroxyl and superoxide radicals (56) produced by the Fenton and Haber-Weiss reaction and are known as "metal-catalyzed-oxidation" (MCO) (57). Oximes are also produced by hydrogen peroxide and the reaction is initiated by abstraction of α -H of amino acid by $\bullet OH$ and carbon-centered radical is formed, which reacts with superoxide radical, hydrogen peroxide and water, to produce carboxylic acid and aldehyde. The overall reaction is represented in Figure 2.

Oxidation of cysteine residues leads to the reversible formation of mixed disulfides between protein thiol groups and low molecular weight thiol, in particular GSH (56). Carbonyl groups are produced by protein oxidation

with ROS (58). Protein oxidation is catalyzed by Fe, Cu, and Al with H_2O_2 i.e. the Fenton-type reaction.

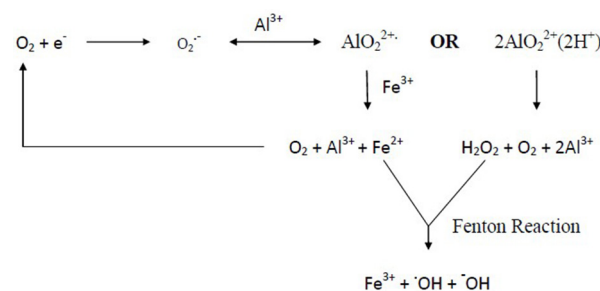
2.6. Advanced Glycation End (AGEs) Formation

The Fenton and Haber-Weiss reactions play significant role in the formation of advanced glycation end products with OH^- acting as a base. Aldehyde (-CHO) or ketone ($C=O$) containing compounds such as glucose can react with amino group ($-NH_2$) of proteins forming the “Schiff’s base”. Then the “Schiff’s base” rearranges to produce the “Amadori products” (Figure 3). These products are responsible for the formation of advanced Glycation end-products (AGEs) through several types of reactions, such as rearrangement, dehydration, condensation, fragmentation, oxidation and cyclization reactions (59).

High reactive carbonyl intermediates such as glyoxal, 3-deoxy-glucosone and methyl-glyoxal are produced by auto-oxidation of glucose, the Schiff’s base or the Amadori products. Then these products can also react with protein free amino group and produce imidazolone, N-q-carboxy-methyl-lysine (CML), N-q-carboxy-ethyl-lysine (CEL), glyoxal-lysine dimer (GOLD) and methyl-glyoxal-lysine

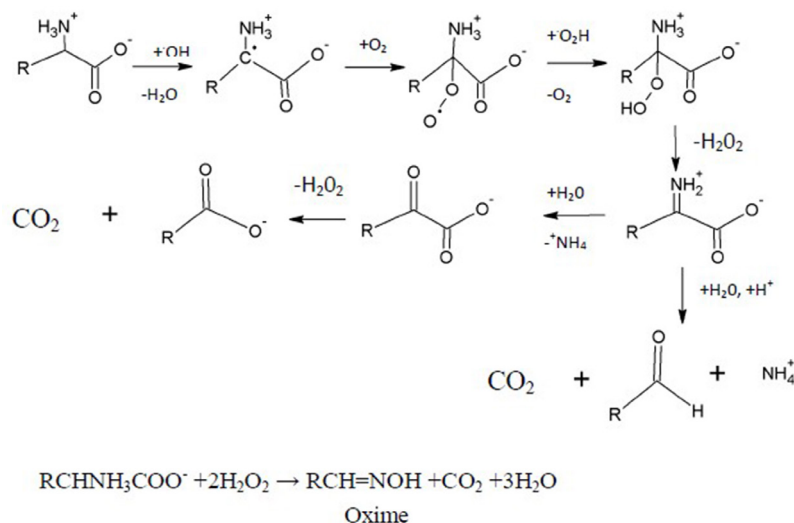
dimer (MOLD) (60-64). AGEs accumulate both intra and extracellular of the aging brain, but in case of AD brain, more AGEs are found in plaque fractions responsible for $A\beta$, than control brain (65).

Figure 2. General Reaction Between Amino Acid and ROS Producing Hydroxyl Radical, Superoxide Anion Radical (or Its Conjugated Acid, HO_2^\cdot), Hydrogen Peroxide by Fenton and Haber-Weiss Reaction



In conclusion protein is converted into corresponding aldehyde, carboxylic acid and oxime by oxidation process.

Figure 3. The Mechanism of Amadori Rearrangement



Amadori product gains their stability by Enol-keto tautomerism. Here $-OH$ acts as a base in this rearrangement. $-OH$ is produced by The Fenton and Haber-Weiss reaction. Six types of AGEs are produced as glucose (AGE-1), carbohydrates like glyceraldehydes (AGE-2), dicarbonyls like glycolaldehyde (AGE-3), methylglyoxal (AGE-4), glyoxal (AGE-5) and 3-deoxyglucosone (AGE-6) (60).

2.7. Effect of ROS on Signaling Pathways

ROS is mainly produced by the Fenton and Haber-Weiss reactions and excess ROS can cause cell death through apoptosis in AD (66). ROS and $A\beta$ can activate ASK1 signaling pathway. ASK1 activates “ASK1 Signalosome” by TNF receptor-associated factor (TRAF) 2 and 6 (67). Then it activates MKK 3/6 pathways, as a result JNK signaling pathway is activated leading to insulin resistance by serine phosphorylation of insulin receptor substrate 1

(IRS 1). Brain imaging (68) revealed the presence of hypoglycemia in Alzheimer’s disease (69-71). Glucose metabolism is regulated mainly by insulin signaling (72), but little is known about the role of insulin in the brain (73). JNK pathway can activate tau phosphorylation and neuronal cell-death (74) as well as inhibiting tyrosine phosphorylation of IRS-1, which results in further cognitive impairment in AD.

3. Results

It is now well established that ROS and RNS (Table 1) can damage different targeted biological molecules such as DNA, protein, lipid through Fenton gated oxidative stress. Figure 4 exhibits synergistic activity of iron and alumi-

num. Here we can see reduction of Fe^{3+} to Fe^{2+} by AlO_2^{2+} , which promotes the oxidative stress through Fenton and Haber-Weiss reaction. Similarly, signaling molecules play essential role in conjunction with Fenton reaction in the pathogenesis of AD as shown in Figure 5.

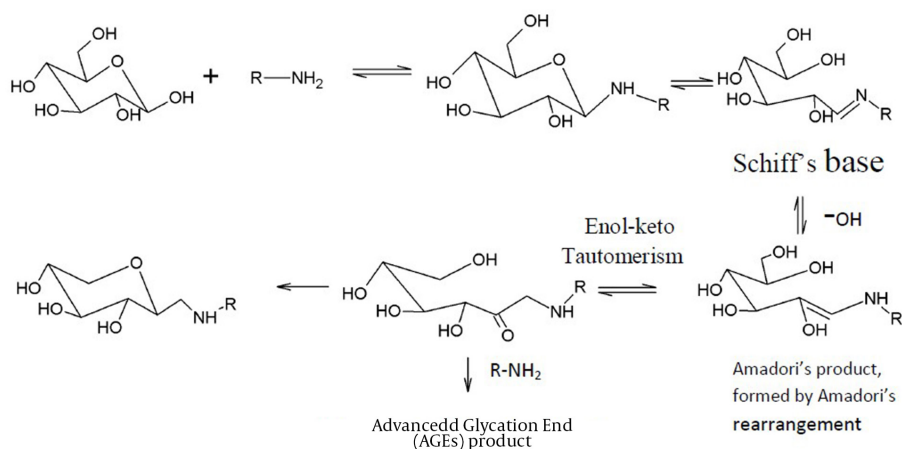
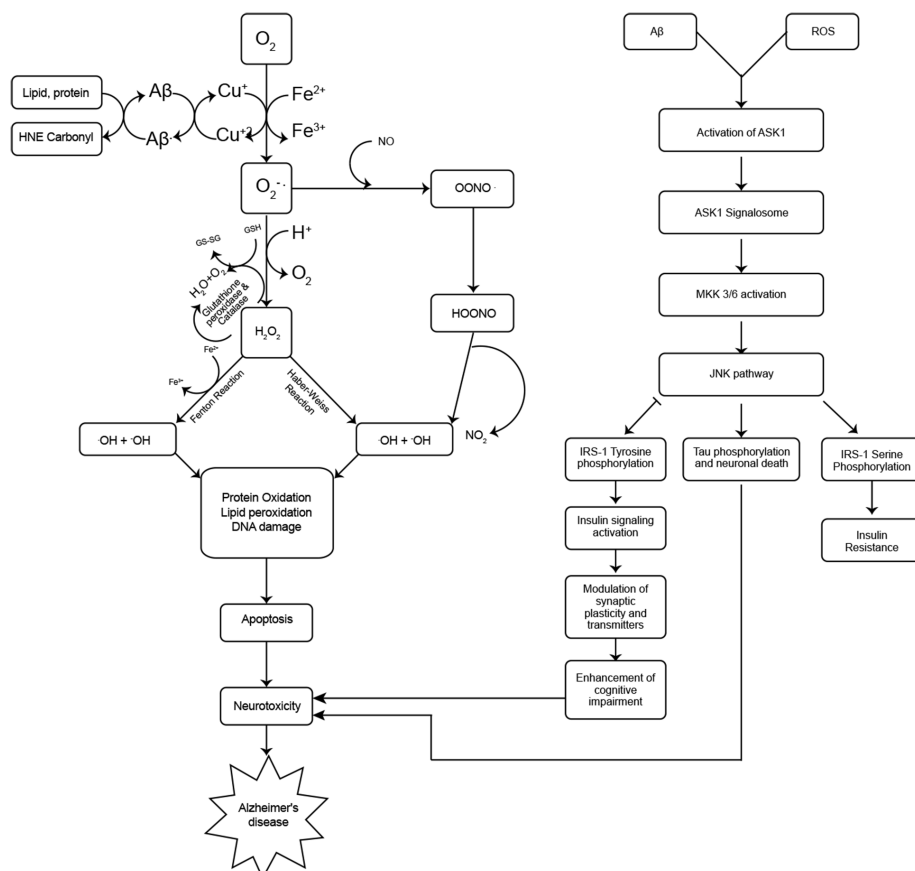


Figure 4. Schematic Diagram for the Formation of Aluminum Superoxide Semireduced Radical Ion and Aluminum Superoxide Complex (43), Which Reduces Fe^{3+} to Fe^{2+} and Promotes Oxidative Stress by Hydroxyl Radical Formation Through the Fenton and Haber-Weiss Reaction.

Figure 5. Schematic Diagram of the ROS and RNS Production and Their Connectivity With ASK1, MKK and JNK Signaling Pathway, Adopted From (66).



These pathways may create Insulin resistance and Alzheimer's disease. ASK1 activates JNK and in a Raf-independent fashion in response to oxidative stress such as oxidative stress, ER stress.

Table 1. Reactive Oxygen and Nitrogen Species Which Enhance Oxidative Stress in Alzheimer's disease (AD); Fe, Cu, Zn and Al Have Catalytic Activity for ROS Production by the Fenton and Haber-Weiss Reaction

Variable	Value
A) Reactive oxygen species (ROS)	
Radical	
Superoxide (anion)	$O_2^{\bullet-}$
Carbonate (anion)	$CO_3^{\bullet-}$
Hydroperoxy	HOO^{\bullet}
Hydroxyl	HO^{\bullet}
Hydroperoxyl	HO_2^{\bullet}
Peroxyl	ROO^{\bullet}
Alkoxy	RO^{\bullet}
Non-Radical	
Hydrogen Peroxide	H_2O_2
Singlet Oxygen	1O_2
Hypochlorous Acid	$HOCl$
Ozone	O_3
B) Reactive Nitrogen Species (RNS)	
Radical	
Nitrogen Monoxide	$\bullet NO$
Nitrogen Dioxide	$\bullet NO_2$
Non-Radical	
Peroxynitrite (anion)	$ONOO^-$
Peroxynitrous Acid	$ONOOH$
Nitrosoperoxycarbonate (anion)	$ONOOCOO^-$
Nitronium (Cation)	$+NO^2$
Dinitrogen Trioxide	N_2O_3

4. Discussion

Mitochondrial dysfunction has a pivotal role in Alzheimer's disease. Production of reactive oxygen species is one of the main reasons of mitochondrial dysfunction. ROS can damage protein, lipid, DNA and can impair glucose metabolism, which is interlinked with insulin signaling. Therefore, there could be an association between Alzheimer's disease and diabetes mellitus. The Fenton and Haber-Weiss reaction should be focused for the treatment of neurodegenerative diseases such as Alzheimer's disease. Antioxidants, metal chelators and free radical scavengers are used for the treatment of AD, but new therapeutic medications could be developed for prevention and treatment of Fenton gated neurological disorders like AD.

Author's contributions

First author; acquisition of data/reference papers and primary drafting of the manuscript, second author; administrative technical and material support and study supervision, corresponding author; mainly study con-

cept and design, critical revision of the manuscript, analysis and interpretation and organization of data, final drafting of the manuscript and study supervision.

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