Iron Toxicity in Neurological Diseases: A Key or Standby

Zahraa Naje [1] [1, 2, 3] Biochemistry Department, College of Medicine, University of Kerbala, Karbala, Iraq

Rana M. Hameed [2*], [1, 2, 3] Biochemistry Department, College of Medicine, University of Kerbala, Karbala, Iraq
**Corresponding author Email*: rana.m@uokerbala.edu.iq

Atheer Hameid Odda [3], [1, 2, 3] Biochemistry Department, College of Medicine, University of Kerbala, Karbala, Iraq

Amer Fadhil Alhaideri [4] [4] Professor of Psychiatry College of Medicine, University of Kerbala, Karbala, Iraq

ABSTRACT

Ferroptosis is a recently identified type of regulated cell death. Specifically, it is a non-apoptotic, iron-dependent, oxidative cell death mechanism that was proposed by Dixon. There are several prospects regarding ferroptosis in the nervous system. Importantly, there is a need for chemical probes or biomarkers capable of elucidating the ferroptosis mechanism to determine its role in the nervous system given the quick cell death occurrence and difficulty in obtaining appropriate neurons. This review would aim to highlighting the role of free iron, their transported such divalent metal transporter 1 (DMT1) and ferritin in Neurodegeneration disease.

Keywords: Ferroptosis, Neurodegeneration disease, Alzheimer's disease, Parkinson disease

Introduction

Cell death in multicellular organisms occurs in different mechanisms, including apoptosis, autophagy, and necrosis (1). The mode of cell death can be generally categorized based on its morphological characteristics, enzymological role and functional characteristics into different types (2). Ferroptosis is a relatively novel cell death type that was first termed by Dixon *et al.* in 2012; mitochondrial shrinking coupled with increased mitochondrial membrane density and degraded mitochondrial crista without nucleation alterationsis the primary morphological characteristic of ferroptosis (3).

It is a mechanism for non-apoptotic, iron-dependent, oxidative cell death characterized by glutathione consumption and lipid peroxides accumulation. Ferroptosis is crucially involved in neurological diseases (4).

Ferroptosis characteristics (iron dysregulation, lipid peroxidation, and inflammation) are considered critical preclinical signs of Alzheimer'sDisease AD and cognitive impairment (5). Lipid peroxidation is considered an early event in AD pathogenesis (6). Specifically, excess iron aggravates toxic amyloid b peptide and hyperphosphorylated tau aggregation; moreover, it directly induces oxidative neuronal damage (7).

Iron interacts with amyloid b and tau through peptide-heme complex formation and thus contributes to ROS generation, which might be involved in the ferroptosis pathway (8). Moreover, brain tissues of patients with AD have increased levels of 4- hydroxynonenal, a lipid oxidation by-product, which contributes to amyloid b accumulation (9).

Ferroptosis is crucially involved in neurological diseases, including neurodegeneration, stroke

and neurotrauma. Elucidating the ferroptosis role in the brain can improve the understanding of neurological disease mechanisms and provide potential prevention and treatment interventions for acute and chronic neurological diseases.

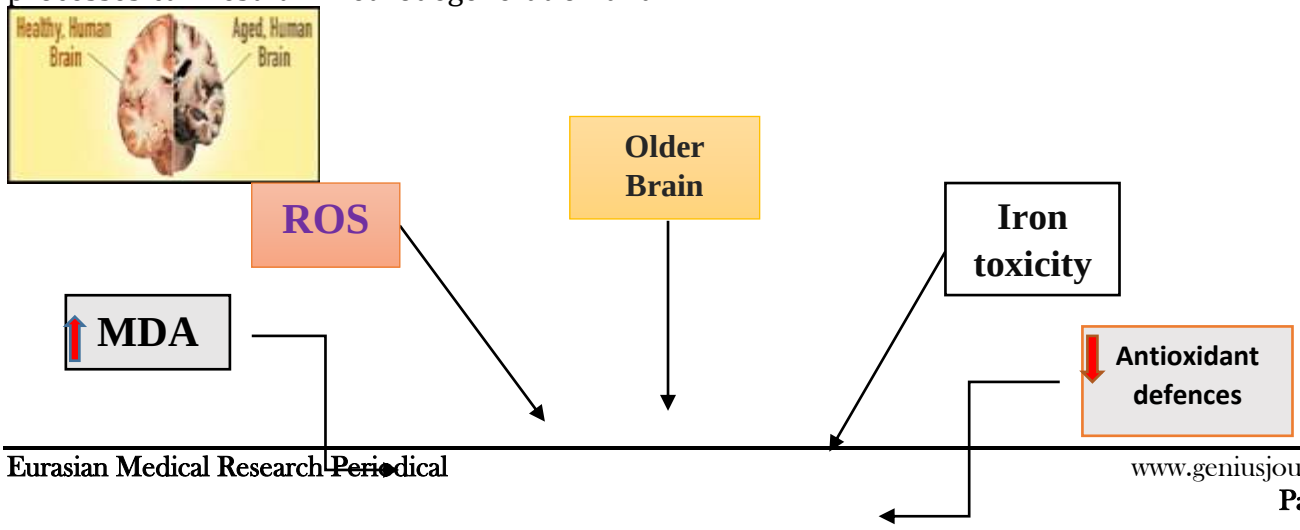
Ferroptosis is essential in the brain and neurological diseases (10). The brain has the highest levels of PUFAs, recognized as lipid peroxide precursors, in the human body (11).

Neurodegenerative diseases (NDDs) are chronic, incurable disorders of the Central Nervous System (CNS) characterized by a progressive decline of synaptic functions and irreversible neuronal loss; with ageing as the leading risk factor, the most prevalent NDDs are Alzheimer's disease (AD) and Parkinson's disease (PD), (12).

These diseases are characterized by the progressive functional loss of neurons in the brain, causing cognitive impairment and motoneuron disability (13). One in ten individuals aged ≥65 has AD, and its prevalence continues to increase. Few or no effective treatments are available for ageing-related neurodegenerative diseases, which tend to progress irreversibly and are associated with enormous socioeconomic and personal costs (14)

Alzheimer's disease (AD) is the most common form of dementia, progressively affecting older people. The dyshomeostasis of biometals and accumulation of toxic metals are usually observed in numerous neurodegenerative diseases, including AD. In the central nervous system, metal imbalance–caused neurotoxic activities are usually linked with decreased enzymatic activities, increased aggregation of proteins, and oxidative stress, where a series of processes can result in neurodegeneration and cell death (15). According to the latest WHO data published in 2020, Alzheimers and Dementia Deaths in Iraq reached 2,429 or 1.66% of total deaths. The age-adjusted Death Rate is 19.16 per 100,000 populations, ranks Iraq 66 worldwide. In 2020 Alzheimers and Dementia Deaths in Iran reached 11,046 or 3.32% of total deaths. The age-adjusted Death Rate is 18.63 per 100,000 population, ranking Iran 74 globally.Turkey reached 17,308 or 4.45% of total deaths. The age-adjusted Death Rate is 19.07 per 100,000 population, ranking Turkey 69 worldwide (16). There are over 50 million people worldwide living with dementia in 2020. This number is almost double every 20 years, reaching 82 million in 2030 and 152 million in 2050. Already 60% of people with dementia live in low and middle-income countries, but by 2050 this will rise to 71%. These figures are estimates based on the best available evidence (17).

While Parkinson's disease (PD) isconsidered one of the most severe health problems in our ageing society, it is a neural disorder that affects people socially and economically. It occurs due to the failure of the brain's dopamine-producing cells to produce enough dopamine to enable the motor movement of the body. This disease primarily affects vision, speech, movement problems, and excretion activity, followed by depression, nervousness, sleeping problems, and panic attacks (18). According to the latest WHO data published in 2020, Parkinson's Disease Deaths in Iraq reached 658 or 0.45% of total deaths. The age-adjusted Death Rate is 4.74 per 100,000 population, ranking Iraq at 59 worldwide(16). A proposed scheme for the Alzheimer's disease markers was presented in (Figure-1)



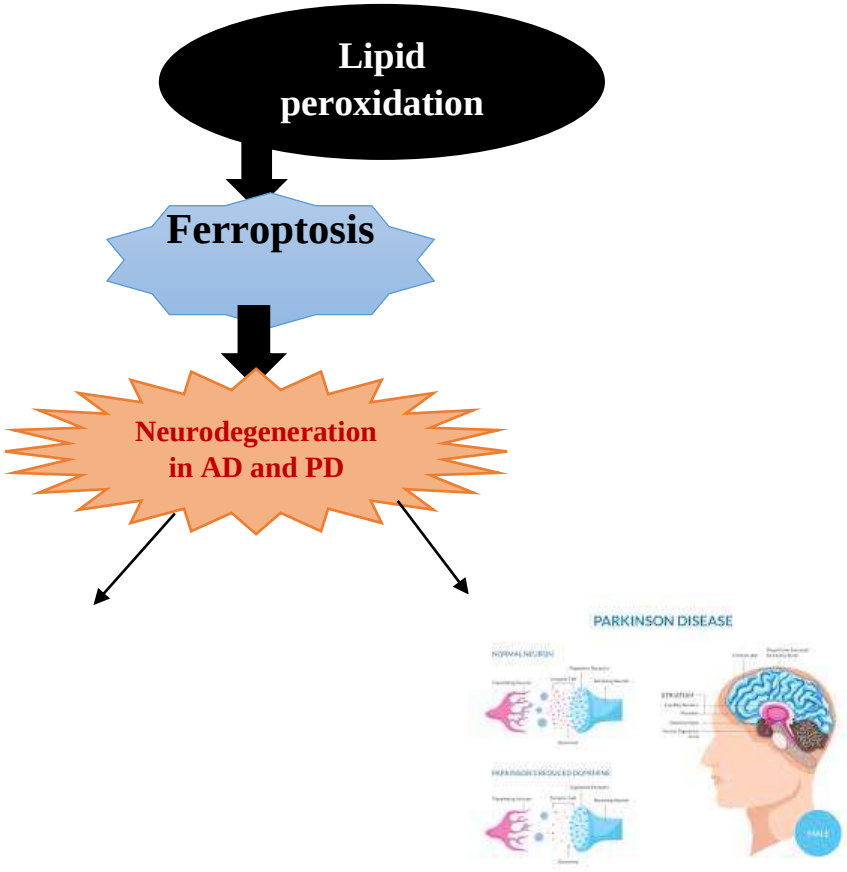
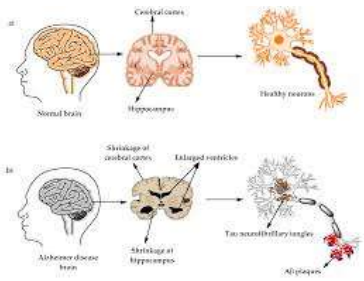


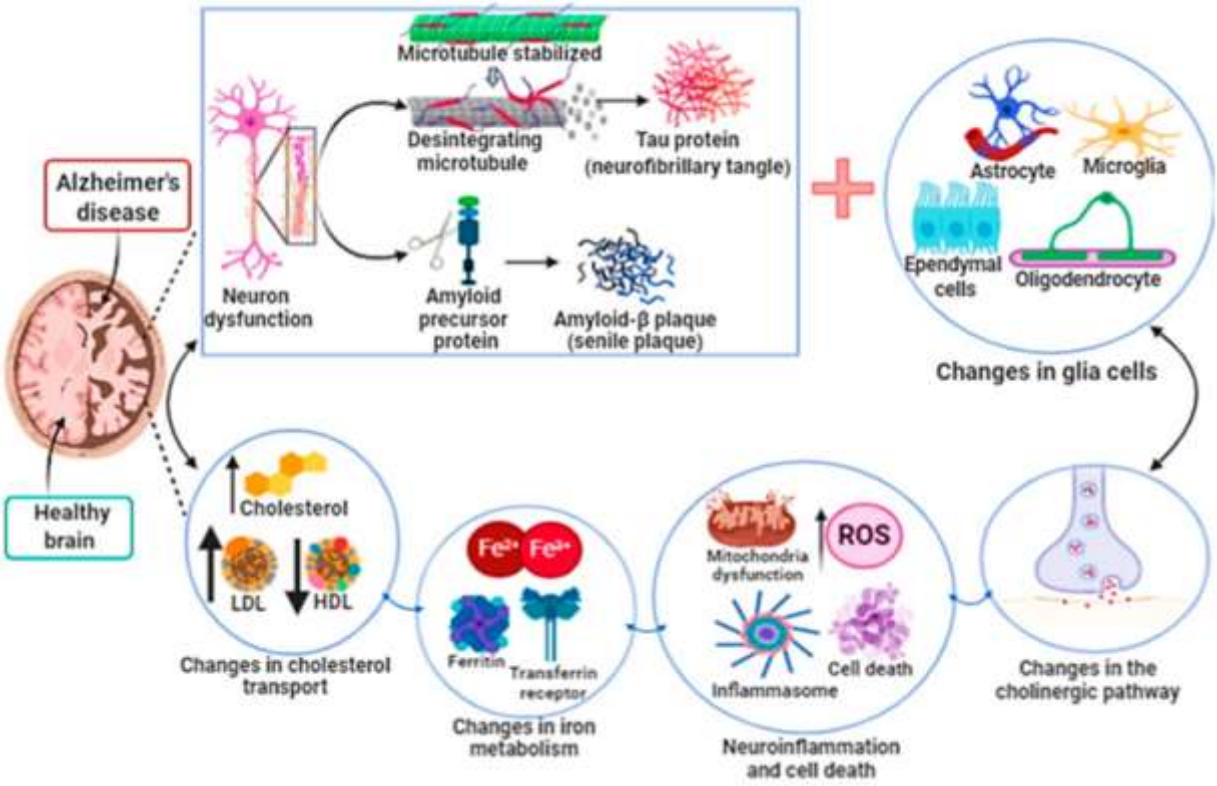
Figure-1 Proposed scheme for the role of iron toxicity, ROS, MDA, older brain and antioxidant defense and their association with Alzheimer's disease and Parkinson disease

Ferroptosis in Neurodegenerative Diseases

In ferroptosis, brain iron, glutathione depletion, and lipid peroxidation build up. This sets off a series of reactions that result in inflammation, neurotransmitter oxidation, impaired neuronal communication, myelin sheath degeneration, dysregulated astrocytes, dementia, and cell death. Additionally, it has been demonstrated that ferroptosis in motor neurodegeneration is linked to poor GPx4 and glutathione system activity (19).

AD is characterized by a gradual dysfunction in the cortical and hippocampus neuronal regions, resulting in both the loss of neuronal function and cell death. The characteristic of AD is the histological presence of internal neurofibrillary tangles (NFTs), which are produced by the hyperphosphorylation of the tau protein and extracellular amyloid (A) accumulation in senile plaques (SPs). Synapse loss and neurotransmitter oxidation are linked to neurocognitive impairment. The rise in oxidative stress, namely an increase in ROS and intra- and extracellular hydrogen peroxides, is to blame for these modifications (20), as present in (Figure-2)





(Figure-2) Ferroptosis in Alzheimer's Disease (21)

The formation of ROS and neurodegeneration in AD is related to iron dyshomeostasis (20). Additionally, Aβ plaques and NFTs have been linked to ageing and alterations in iron metabolism (22). iron deposition has been linked to the misfolding of Aβ plaques and NFTs(23).

NFTs and Tau protein formation are both influenced by iron. Tau phosphorylation is induced and controlled by iron (24). Tauopathy is the name for the relationship between NFT and neurodegenerative dysfunctions (25).

While in the case ofParkinson's Disease, The striatum loses dopamine due to the slow and gradual degeneration of dopaminergic neurons in the pars compacta of the substantia nigra (SNpc), which is linked to a systematic and progressive iron buildup. Neuromelanin is also absent, and intracellular Lewy bodies with aggregated α -synuclein as their primary component appear (26). As PD progresses, oxidative stress, lipid peroxidation, and mitochondrial dysfunction rise along; with the glutathione systems' loss of antioxidant enzymes. These related conditions cause neuronal death and impair the organism's capacity to operate (27).

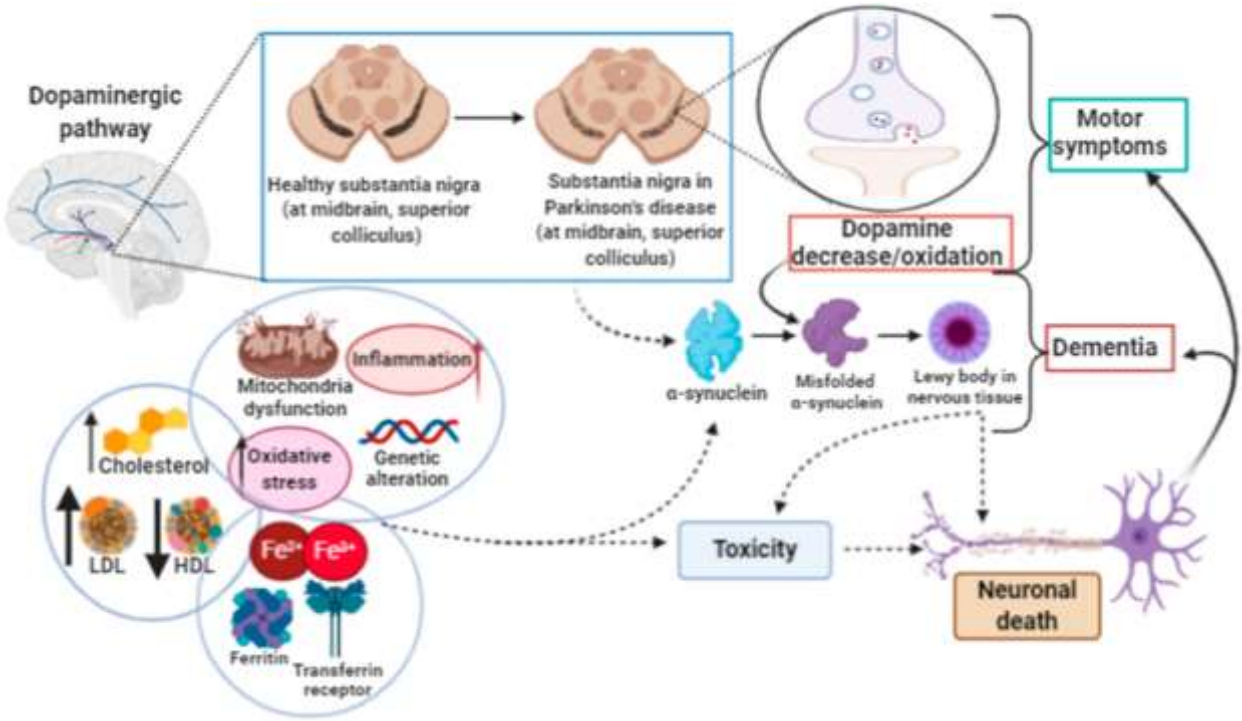
It has long been known that iron and PD are related. Daily exposure to high iron levels raises the likelihood of developing Parkinson's disease (PD). Magnetic resonance imaging (MRI) also showed that PD patients' substantia nigra and globus pallidus have higher iron concentrations. This rise was related to the progression of the illness, neurodegeneration, and the degree of moving weakness (28).

The association between iron metabolism and Parkinson's disease has also been strengthened by discovering multiple genes and proteins associated with the iron metabolism of brain cells in PD patients (29).

The molecular processes underlying the interplay between PD with ferroptosis cell death are becoming increasingly clear thanks to an abundance of new findings since the pathogenic consequences of the proteinα -synuclein, which is widely expressed in the nervous system andclosely connected to the pathophysiology of PD (30).

Additionally, it has recently been demonstrated that α -synuclein aggregation, a characteristic of Parkinson's disease (PD), causes the generation of ROS, which is then followed by lipid peroxidation in an iron-

dependent way, increasing calcium influx and, ultimately, cell death (31). (Figure3)



(Figure- 3) Ferroptosis in Parkinson's Disease (32)

Knowledge gap

Current research on ferroptosis in neurological diseases is mainly focuses on the critical pathways of ferroptosis. At the same time, ferroptosis was found to play a bidirectional regulation role in neurological diseases. Therefore, the specific regulatory mechanisms of ferroptosis in neurological diseases still need further exploration to provide new perspectives for applying ferroptosis in neurological diseases. Mainly, there is an urgent need for a specific ferroptosis biomarker in such cases.

Research on ferroptosis is still in the initial stage, and many obstructions remain to be resolved. It is essential to underlying the mechanism of the bidirectional regulation of p53 in ferroptosis, which is still unclear. Iron has been proven to be criticalin ferroptosis, which could catalyze lipid peroxidation through a Fenton reaction to mediate ferroptosis. However, other studies have also shown that other metal elements, such as copper, can participate in the redox reaction and participate in ferroptosis. Therefore, are there other metal ions involved in regulating cell ferroptosis? Is iron necessary for ferroptosis, or can other elements replace it?

Currently, known upstream genes involved in regulating iron metabolism, including FPN, and TFR1 can affect the occurrence of ferroptosis, but it is essential to specify the molecular mechanism, which is downstream iron metabolism.

A combination of multiple biomarkers may help detect ferroptosis cell death in time. The challenge remains how to transform primary research findings into clinical applications. Solving these challenges requires a further understanding of ferroptosis's molecular mechanisms and signal transduction. Ferroptosis regulatesthe inflammatory response, but the specific mechanism of ferroptosis promoting inflammation is currently unclear.

List of abbreviation

AD: Alzheimer's Disease
PD: Parkinson's disease
CNS: Central Nervous System
FPN: 4-Fluorophenol
GPx4: Glutathione peroxidase 4
MDA: Malondialdehyde
MRI: Magnetic resonance imaging
NDDs: Neurodegenerative diseases
NFTs: Neurofibrillary Tangles

p53: protein 53
PUFAs: polyunsaturated fatty acids
ROS: Reactive oxygen species
SNpc: Substantia nigra pars compacta
SPs: Senile Plaques
TFR1: Transferrin receptor protein 1
WHO: World Health Organization
DMT1: divalent metal transporter 1
Aβ: Amyloid beta

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