Journal of Neuroscience and Neuropharmacology 2023, Vol. 9, Issue 01, 001-002

Links between Iron Metabolism, Ferroptosis, and Alzheimer's Disease

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Received: 02-Jan-2023, Manuscript No. NCOA-23-96174**; Editor assigned:** 04-Jan-2023, PreQC No**.** NCOA-23-96174 (PQ); **Reviewed:** 13-Jan-2023, QC No. NCOA-23-96174 (Q); **Revised:** 15-Jan-2023, Manuscript No. NCOA-23-96174 (R); **Published:** 23-Jan-2023, DOI: 10.4172/2469-9780.2023.9.1.188

Abstract

For many biological processes in mammals, iron is a crucial transition metal. Several coordination mechanisms, including as absorption, utilization, recycling, and storage, are used to control iron metabolism. As a result of intracellular iron retention brought on by iron dyshomeostasis, free oxygen radicals can harm cells, tissues, and organs. Brain iron excess has been linked to the pathogenic process of neurodegenerative diseases, including Alzheimer's Disease (AD), according to a number of studies. The fundamental mechanisms, nevertheless, are still not completely understood. We may gain a fresh perspective from ferroptosis, a newly identified iron-dependent form of cell death that is unique from apoptosis, necrosis, autophagy, and other types of cell death. Here, we want to review the state of our understanding of iron metabolism.

Keywords: Alzheimer's disease • Neurodegenerative diseases • Ferroptosis

Introduction

Iron is the most common transition metal in life and the second most common metal in the earth's crust after aluminium. By taking on multiple oxidation states, iron participates in a number of essential biological activities, including as oxygen transport, DNA synthesis and repair, respiratory activity, myelin production, and cellular function. At the systemic and cellular levels, iron homeostasis is maintained by a variety of processes, including hepcidin and Iron Regulatory Proteins (IRPs). When iron homeostasis is disturbed, there may be an excessive buildup of iron inside of cells, which can lead to oxidative stress and the production of free radicals, which can damage proteins, lipids, and DNA.

Iron dyshomeostasis has been linked to the aetiology of Alzheimer's Disease (AD), according to a growing body of research. Through imaging and histologic analyses, iron depositions in particular brain areas have been demonstrated in AD patients. A recently discovered non-apoptotic form of cell death known as ferroptosis is characterized by the buildup of lipid Reactive Oxygen Species (ROS) that is iron-dependent. Recent research indicates that ferroptosis is crucial for neuronal death and neurological disorders such Friedreich's ataxia, Parkinson's disease, Huntington's disease, and Traumatic Brain Injury (TBI). These research provide us fresh viewpoints. As a result, we examine the current understanding of iron metabolism and ferroptosis as well as how these factors affect AD.

Due to its ease in giving and accepting electrons to take part in oxidation-reduction events, iron is an essential element for a wide range of fundamental biological processes. But when there is too much "free" iron present, it is equally poisonous. In fact, this redox-active iron may catalyze the Fenton reaction, which damages cells by destroying their lipids, proteins, and nucleic acids. The central nervous system's production of myelin and neurotransmitters depends heavily on iron. However, high levels of iron in the brain have been linked to numerous neurodegenerative conditions, including multiple sclerosis, Alzheimer's disease, Parkinson's disease, and HD.

Additionally, neurological impairments and mental retardation can readily result from iron deficiency in babies and the growing brain. As a result, a complex network of mechanisms comprising absorption, utilization, recycling, and storage must be used to elegantly manage iron metabolism. A number of proteins, Including Ferritin (FTH1), Transferrin (Tf), Transferrin Receptor 1 (TfR1), Divalent Metal Transporter 1 (DMT1, SLC11A2), Ferroportin (FPN1), and hepcidin, are involved in this intricate, tightly controlled process.

The Blood-Brain Barrier (BBB), which distinguishes the brain from other tissues and organs by being a special structure, closely controls the flow of ions, chemicals, and cells between the blood and the brain. As a result, the Tf/TfR1 pathway, which depends on the BBB, is the principal channel by which brain iron is absorbed, and the endothelial cells of the BBB are the essential location for controlling brain iron uptake. According to research, Tf is the iron carrier that transports ferric iron to erythrocyte precursors and other tissues. However, ferrous iron must first undergo oxidation to ferric iron by the multi-copper ferroxidase enzyme hephestin before it can attach to Tf. In endothelial cells' luminal side, TfR1 is abundantly expressed.

Thus, Tf-bound serum iron in circulation first binds to its receptor (TfR1) and is taken up through endocytosis. Ferric iron is then released from Tf and reduced to ferrous iron by ferric reductase Six-Transmembrane Epithelial Antigen of Prostate 3 (STEAP3) in the acidic endosome, where it is then transferred by DMT1 for metabolic synthesis or to be stored with ferritin in the cytoplasm. Iron is primarily transported by the metal transporter DMT1 from the endosome to the cytoplasm. Additionally, FPN1 may transfer iron to the extracellular environment. In mammals, FPN1 is the only intracellular iron exporter that is currently known, and it is essential for the export of cellular iron. Additionally, the iron-regulating hormone hepcidin, which is mostly produced and released by the liver, regulates FPN1.

However, the manners that various cell types absorb iron vary. Iron can be taken up by neurons and microglia via the Tf/TfR1 route or by NTBI via the luminal DMT1-dependent pathway. Recent research indicates that the primary mechanism by which oligodendrocytes absorb iron is the binding of H-ferritin to the H-ferritin receptor (Tim-1/2). Astrocytes can get iron through their end-foot processes in addition to the Tf/TfR1 or DMT1 route. Thus, iron levels in the brain are properly controlled to support regular neuronal activity.

Ferroptosis

A newly identified kind of controlled cell death called ferroptosis is characterised by iron-dependent lipid peroxidation, which in turn causes oxidative stress and cell death. Apoptosis, necrosis, autophagy, and pyroptosis are different types of cell death from ferroptotic cell death in terms of morphology, biochemistry, and genetics. The primary characteristics of ferroptosis in cytological alterations are diminished or absent mitochondrial cristae, condensed mitochondrial membrane, and reduction of the mitochondrial volume. As a result of this redox

dyshomeostasis, this is characterized by a buildup of iron-dependent ROS, a drop in glutathione levels, and the inactivation of Glutathione Peroxidase 4 (GPX4), ferroptosis results in cell death.

Ferroptosis is a new form of cell death that results from iron accumulation and lipid peroxidation in cells. It involves depletion in the antioxidant enzymes resulting in lipid peroxidation and oxidative stress. It is an iron-dependent and oxidative damage induced cell death involving cytological changes such as decreased mitochondrial cristae and damaged mitochondrial membranes. These cell abnormalities resulted from the loss of selective permeability of plasma membrane due to intense membrane lipid peroxidation and the occurrence of oxidative stress. Ferroptosis is an exceptional metabolic process involving amino acids, lipids, NADPH, and microelements. However, cysteine depletion, GPX4 inactivation, and iron overload causes cells to undergo metabolic stress or ferroptotic cell death.

The main mechanism for the spread of ferroptosis is the peroxidation of proteins, nucleic acids, and lipids, which is promoted by intracellular iron buildup. This process can create ROS and lead to oxidative stress via the Fenton reaction. It's interesting to note that inducers of ferroptosis were discovered before the name ferroptosis was ever defined. First, scientists unanticipatedly discovered that the tiny chemical erastin caused non-apoptotic cell death in tumor-causing cells. Then, two ras-selective lethal small molecules (RSL3 and RSL5) that caused non-apoptotic and iron-dependent oxidative cell death were filtered out. Desferrioxamine, an iron chelator, and vitamin E, an antioxidant, may both stop this kind of cell death, which had characteristics with a prior type of cell death brought on by erastin. This unusual non-apoptotic cell death was given the term ferroptosis in 2012.

Cite this article: Xiao, N. Links between Iron Metabolism, Ferroptosis, and Alzheimer's Disease. J Neurosci Neuropharmacol. 2023,9(1), 001-002