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Therapeutic potential of Iron and Zinc for brain health: A review

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Trace elements with various roles in metabolic processes as a cofactor or catalysts in enzymatic functions are required in milligrams. In this review, the activity of two trace elements, Fe and Zn, on brain activity is explained. Iron is a significant element for improving learning and memory, Parkinson's disease, Alzheimer's disease, depression, anxiety, and hypoxia. Low ferritin levels in premature infants result in poor motor skills and altered gene expression. Hemoglobin production is reduced due to lack of iron in cells, which increases pro-inflammatory cytokine interleukin-6 and causes depression in postpartum women. Zinc is an essential trace element that plays a substantial role in various biochemical processes such as growth and development, brain activity, immunity, lipid metabolism, and controls external and internal behaviors. Deprivation of zinc leads to depression and anxiety as the alteration in the expression of the BDNF (brain-derived neurotrophic factor) gene occurs. Low zinc levels and high glucocorticoid levels can be a reason for aggression, impulsiveness, conduct and control problems. Reduction in zinc uptake by the inhibition of ZnT3 (zinc transporter-3) leads to impaired learning and memory.

Keywords: iron, zinc, depression, anxiety, disease

INTRODUCTION

Trace elements are the chemical components needed in small quantities (milligrams or micrograms) by the human body. These elements are mostly minerals, constituting <0.01% of the body mass. (Aliasgharpour & Rahnamaye Farzami, 2013) Despite their small contribution to the body mass they have tremendous roles in the body. Many of them assist metabolic processes by working as a catalyst or cofactor for different enzymes. The synthesis of structural and functional proteins also depends on these elements. Either deficiency or accumulation of these elements contributes to diseases. Elements, like selenium, zinc and iron, function as an important part of the enzymes and facilitate their respective reactions. Few of the trace elements become electron donor or acceptor in redox reactions, thus impacting the production and utilization of energy. Some elements mediate significant biological processes by aiding the bonding of molecules (on cell membranes) to their receptor sites, preventing or allowing particular molecules to move in or out of the cell by changing the ionic nature or structure of the membranes, and causing the expression of

genes, which lead to the synthesis of proteins important for biological processes.(Prashanth, Kattapagari, Chitturi, Baddam, & Prasad, 2015) The ability to keep a balance of body conditions (including pH, temperature, and amount of a certain substance such as trace elements) within a specific range is called homeostasis. It includes maintaining the content of elements, irrespective of their intake, which comprises of their absorption, storage, and excretion. These processes vary for different trace elements. The homeostasis of trace elements which exist as cations (such as, zinc, copper) is regulated during their absorption from gut. Elements existing as anions are absorbed completely and freely from the intestine. So, their homeostasis is controlled by the excretion through bile, urine, sweat and breath. In addition to this, the presence of inapt reactive trace elements is prevented through the storage of these elements in inactive forms. To prevent deficiency, the release of an element from the reserves can also be significant.(Aliasgharpour & Rahnamaye Farzami, 2013)

Iron, along with the other micronutrients, carries out significant functions in infants to ensure healthy growth and development. Otherwise, iron deficiency anemia can occur in infants due to depleting sources of iron in the body. Iron supplementation is found to be significant for improving the hematological measurements and anemic status in preterm infants as compared to the placebo. More studies are required to establish the effect of iron supplementation on neurodevelopment (Long et al., 2012). Iron intoxication causes impairment in DNA sequencing and lipid peroxidation and may result in central nervous system (CNS) damage. Iron deficiency has severe effects on mental health. It makes one prone to defects in the myelin sheath and improper neurotransmission. Proper iron intake is compulsory to avoid such unhealthy effects (Muñoz & Humeres, 2012). Iron is also found to be significant for declining the chances of attention-deficit/ hyperactivity disorder (ADHD). Iron deficiency contributes to ADHD occurrence based on different pieces of evidence. Iron performs its action as a co-factor for those enzymes involved in the synthesis and breakdown of monoaminergic neurotransmitters—progress the ADHD. Iron deficiency makes a man vulnerable to genetic variations by causing a decrease in the dopamine transporter gene expression. Iron insufficiency may prompt dysfunction in the basal ganglia leading to ADHD. Iron is crucial for healthy brain biochemistry (Cortese et al., 2012). Iron homeostasis plays a significant role in brain activities, which otherwise can cause neurotoxicity. Iron forms complex with metalloproteins to avoid damage from free radicals. The alteration in iron metabolism can lead to oxidative stress that promotes Alzheimer's disease and Parkinson's disease (Belaidi & Bush, 2016; Ward, Zucca, Duyn, Crichton, & Zecca, 2014)**.**

Zinc is found to be an anti-depressant element. Zinc supplementation with anti-depressant drugs provides benefits to reduce depression (Ranjbar et al., 2014). Zinc has importance for gene expression and synthesis of protein. Its deficiency affects the transcription process. It has been found that zinc deficiency suppresses the production of vitamin A transport protein, serum retinol-binding protein (Kimball, Chen, Risica, Jefferson, & Leure-duPree, 1995). Zinc is significant to maintain the protein balance for viscera organs and helps to maintain muscle mass. The improvement in levels of pre-albumin and retinal-binding proteins is seen in traumatic brain injury patients who were given zinc supplementation. In this way, zinc supplementation improves the outcomes in traumatic brain injury patients (Cope, Morris, & Levenson, 2012). Zinc deficiency is the reason behind multiple psychiatric disorders. Those schizophrenic patients supplemented with “Ziman drops”, consisting of 10% zinc sulfate with 0.5% manganese chloride, had better results. Furthermore, zinc is significant for many cellular processes, activities of many enzymes, and improve synaptic transformation (M Grabrucker, Rowan, & C Garner, 2011).

Classification of trace elements:

According to W.H.O., about 19 trace elements have been categorized into 3 classes, these are as follow:

1. Essential: zinc (Zn), copper (Cu), selenium (Se), chromium (Cr), cobalt (Co), iodine (I), manganese (Mn),and molybdenum (Mo)
2. Probably essential
3. Potentially toxic (Bhattacharya, Misra, & Hussain, 2016)

Essential trace elements:

These are needed by humans in range 50mcg – 18mg/day. Borderline or severe deficiency (or toxicity) of these elements can result in different diseases or health conditions. These elements function as a catalyst for various enzymes

responsible for metabolic processes.

Probably essential elements:

Not much is known about these elements and they are assumed to be less beneficial for the human health. Manganese, nickel, silicon, boron, and vanadium are included in this category.

Potentially toxic elements:

These are abbreviated as PTEs. These have lethal health affects if consumed (or present) in large quantities. Fluoride, cadmium, lead, and mercury are included in this category.(Aliasgharpour & Rahnamaye Farzami, 2013)

Frieden also categorized the trace elements into three classes depending upon their quantity in the tissues.

a. Essential: B (boron), Co (cobalt), Cu (copper), Fe (iron), I (iodine), Mo (molybdenum), Mn (manganese)
b. Probably essential: Cr (chromium), Se (selenium), F (fluorine), Ni (nickel), V (vanadium)
c. Physically promotive: Li (lithium), Br (bromine), Sn (tin), Si (silicon), Ti (titanium)

(Prashanth, et al., 2015)

Iron:

Iron has an important role in the mitochondrial function, myelin production, transport of oxygen and oxidative phosphorylation. Abnormal iron metabolism can cause oxidative damage. During aging, accumulation of iron is associated with cognitive and motor impairment (Ward, et al. 2014).

Table 1: RDA of Iron and Zinc (mg/day)

	Iron:		Zinc:	
Age:	**Male:**	**Female:**	**Male:**	**Female:**
0-6 months	0.27	0.27	2	2
7-12 months	11	11	3	3
1-3 years	7	7	3	3
4-8 years	10	10	5	5
9-13 years	8	8	8	8
14-18 years	11	15	11	9
Pregnancy:	-	27	-	12
Lactation:	-	10	-	13
19-30 years	8	18	11	8
Pregnancy:	-	27	-	11
Lactation:	-	9	-	12
31-50 years	8	18	11	8
Pregnancy:	-	27	-	11
Lactation:	-	9	-	12
50-70 years	8	8	11	8
>70 years	8	8	11	8

Sources of iron

Table 2: Iron quantity in Fruits, Vegetables, Meat & Dairy Products (mg)

Fruits And fruit juices					
Name	**Quantity**	**Iron**	**Name**	**Quantity**	**Iron**
Apple juice	½ c	0.31	Apple slices (peeled)	½ c	0.16
Apple with peel	1	0.16	Apricot (fresh)	4 items	0.54
Avocado	½ c	0.66	Banana (fresh whole)	1 item	0.30
Blackberries (raw)	½ c	0.45	Blueberries (raw)	½ c	0.20
Cherries (sweet, raw)	½ c	0.26	Cranberries (raw)	½ c	0.13
Dates (whole)	¼ c	0.45	Figs (raw, medium)	2 items	0.36
Grapefruit juice	½ c	0.45	Grapefruit raw	½ c	0.09
Grapes	½ c	0.13	Raisins, seeded	¼ c	1.06
Guava, raw	1 item	0.14	Lemon, raw	1 item	0.75
Mango	½ c	0.10	Melon	½ c	0.17
Watermelon	½ c	0.18	Orange (raw)	1 item	0.13
Orange (sections)	½ c	0.09	Papaya	½ c	0.07
Peach (raw, medium)	1 item	0.37	Pear (raw)	1 item	0.28
Pineapple (raw)	½ c	0.22	Pomegranate	1 item	0.46
Prunes, dried	2 items	0.16			
Vegetables					
Name	**Quantity**	**Iron**	**Name**	**Quantity**	**Iron**
Artichoke (boiled)	1 item	0.73	Asparagus (boiled)	½ c	0.81
Beets (whole, boiled)	2 items	0.79	Broccoli (raw)	½ c	0.33
Cabbage (boiled)	1 c	0.24	Carrots (baby, raw)	8 items	0.71
Cauliflower (boiled)	½ c	0.19	Cucumber	¼ item	0.20
Lettuce (leaves)	11 items	1.02	Okra (boiled)	½ c	0.22
Onion (chopped, boiled)	½ c	0.24	Spinach (chopped, boiled)	½ c	3.21
Tomato (ripe, fresh)	1 item	0.33	Turnips (chopped, boiled)	½ c	0.58
Watercress	1	0.06			
Meat and Meat Products					
Beef (breakfast strips, cooked)	2 slices	0.71	Ground beef	3 oz.	2.0
Lamb chop	3 oz.	1.53	Chicken (canned)	2 oz.	0.89
Chicken breast (fried)	3 oz.	1.05	Fish (Salmon), raw	3 oz.	0.29
Broiled or baked with butter	3 oz.	1.02	Egg (fried)	1	0.91
Dairy Products:					
Fluid milk (low fat, 1%)	1 c	0.07	Cottage cheese (low fat, 1%)	½ c	0.15
Yogurt (plain, low fat)	1 c	0.19			

Its deficiency not only causes the changes in hippocampus but also alters the function and interaction of prefrontal cortex of amygdala (Muñoz & Humeres, 2012). Therefore, iron should be consumed according to the RDA to prevent toxicity and deficiency (Trumbo, Yates, Schlicker, & Poos, 2001).

Iron also plays an important role in synaptic plasticity and synaptogenesis. However, deficiency leads to the learning and memory problems.

Metabolism:

Iron can also be a toxic substance because it catalyzes the propagation of reactive oxygen specie and formation of free radical under aerobic conditions (Wang & Pantopoulos, 2011). Reversible oxidation/reduction reaction of Fe^{+2} and Fe^{+3} can transfer single electron from iron redox couple. Majorly body's iron is transported and circulated by the co-protein transferrin (Tf). However, only 1% iron is non Tf bond. Brain capillary endothelial cell (BCESs) transports Fe_2 Tf to blood brain barrier (BBB), which prevents Fe_2 Tf diffusion. Following the endocytosis mechanism by BCESs, Tf binds to Tf receptors and the prevention of Non-Tf bound iron (NTBI) occur. Protein divalent transporter-1 (DMT1) can export iron from endosome (Hare, Ayton, Bush, & Lei, 2013).

Haem iron uptakes may take place by HCP1. Astrocytes accumulate iron exogenously and uptake Tf-bound ferric iron through Tf to TfR complex. This ferric iron is reduced to ferrous ion which is then exported to cytosol via DMT1. Low-molecular- mass ions or other haem generated can enter into the cell ion pool, where they can be used as haem group or iron sulfur (Fe-S) clusters. However, excess iron can be stored in redox-inactive form (Hohnholt & Dringen, 2013).

Learning and memory:

Early life iron deficiency effects three major functions of the brain including, affect, speed of processing and memory and learning. Iron deficiency directly relates to the hippocampus development by altering the intracellular signaling pathway, structure and transcriptome (Fretham, Carlson, & Georgieff, 2011). Iron deficiency is characterized by the depleted iron stores, reduction in the iron depending oxidative enzyme concentration, and hemeproteins that leads to the poor methylation and dendritogenesis, as hemeprotein is required for the proper development of cortical and hippocampal region development (East et al., 2018). During perinatal period, iron deficiency causes alteration of gene expression critical for development and function of hippocampus. Premature infants with low ferritin level have fine motor skills and lower language ability (Radlowski & Johnson, 2013). An experimental trail has been taken on piglets in pre-weaning stage. One group receives 200mg iron dextran injection and fed with control milk (88mg Fe/kg) while other group receives the iron deficient milk (21mg Fe /kg). At the age of 7.5 weeks, all the piglets received the normal diet with 190-240 mg Fe/kg. After the treatment, the blood iron level restored to the normal but impaired long term memory at reversal and acquisition trail has been shown (Antonides et al., 2015).

Parkinson's disease:

Parkinson's disease is a neurodegenerative disorder characterized by the alteration of iron level in the brain. The mechanism includes the oxidative stress, toxicity of iron in brain, neuro-inflammation, and mitochondrial dysfunction (Guan et al. 2017). It can also be caused by the loss of dopaminergic neurons which play an important role in the protecting striatum and substantia nigra (Zhang et al. 2010). Iron retention occurs in specific nuclei of the brain while the other regions remain unaffected (Hare & Double, 2016). Substantia nigra pars compacta are more vulnerable to neuro-degeneration because of the increased level of iron and dopamine in this region. Abnormalities of iron distribution occur throughout the basal ganglia (Hare et al. 2014).However, the degeneration of other basal ganglia neurons occurs, extending throughout the olfactory bulbs (Hare & Double, 2016) . Iron accumulation in Parkinson's disease is also characterized by the genetic mutation in the brain-iron homeostasis.Ceruloplasmin (a copper-binding protein in the plasma has a role in cellular iron export by oxidation of iron) can reduce in the genetic disorder such as in aceruloplasminemia. (Ayton et al. 2014). The oxidative stress of the brain increases due to the unbound iron because it interacts with the hydrogen peroxide (H_20_2) which results in the formation of hydroxyl free radicals in the brain (Weinreb, Mandel, Youdim, & Amit, 2013). Autoxidation produces the $OH^{\cdot}$, as a result of reactive Quinone specie or by the monoamine A and B activity (has a role in dopamine catabolism) (Hare, et al. 2014). Microglia Activation leads to neuro-inflammation which causes progressive degeneration of

neurons and dopaminergic neurons' death in substantia nigra (Yu et al. 2013) .Mitochondria have a role in iron metabolism and synthesis of iron-sulphate clusters and heme for cell functioning. Mitochondrial dysfunction leads to decreased ATP production and reduction in the synthesis of iron-sulphate cluster (Isaya, 2014) . Lacto transferrin receptor (Lfr-iron binding glycoproteins) in neurons works as transporting iron-containing ferritin across neural membrane. Lfr expression in midbrain indicates the Parkinson's disease. (Salvador, 2010)

Alzheimer's disease:

Disturbance in iron metabolism can cause Alzheimer's. It may be at cellular level, iron uptake, intracellular metabolism or regulation. Iron which is a redox metal can cause the production of reactive oxygen specie (Quintana et al., 2006). In Alzheimer's, iron interacts with amyloid-B (AB) peptide that leads to aggregation and production of hydrogen peroxide (H_20_2) (Maynard et al. 2002). An experiment was conducted on mice (on amyloid precursor protein and cortical neurons) where both vivo and vitro were exposed to iron sulfate. The results show an increase in iron load (Becerril-Ortega, Bordji, Fréret, Rush, & Buisson, 2014). Ferritin (Ft), a protein, and hemosiderin (Hm) have a role in the storage of iron especially non-heme iron in the redox-inter form. Ferritin's two composition forms, heavy polypeptides (Ft-H) and lighter polypeptides (Ft-L), can normally increase with age; however their ratio in substantia nigra region can decrease. Ft is abundantly present in the nucleus and cytoplasm of oligodendrocytes (Quintana, et al., 2006). However, ferritin cellular uptake can be reflected by secretion and expression of glia (Ayton et al. 2015). Excessive iron in brain contributes to abnormal accumulation of protein in brain which also causes Alzheimer's. (Bartzokis et al. 2007). In Alzheimer's disease, iron affects the cerebral cortex tissues. Through MRI, an elevated level of non heme iron is detected. Majorly, iron induces the oxidative stress to the amyloid-b peptide (Barnham & Bush, 2008). An increase of iron in cortical region is also examined in Alzheimer's disease. Ferritin level in the brain can be reflected by cerebrospinal fluid (Ayton, et al. 2015). Neuro-inflammation due to iron can cause changes in glial scar (Ong & Farooqui, 2005). Hepcidin is a liver derived hormone which regulates iron homeostasis. Low hepcidin level is associated with high iron load. Reduction of hepcidin expression has been notified in the brain especially in hippocampal lysates. Other protein, ferroportin works in exporting iron from cell to plasma. Reduction in ferroportin is associated with the senile plaque formation and Alzheimer's (Raha, Vaishnav, Friedland, Bomford, & Raha-Chowdhury, 2013).

Iron in depression:

Decrease in iron intake can lead to depression (Li, Li, Song, & Zhang, 2017). Depression is caused by inflammation, oxidative stress, and low blood cell production due to lack of iron and neurotransmitter production. Pro-inflammatory cytokine, interleukin-6, is increased due to low hemoglobin level (Rybka et al. 2013). Iron works as a cofactor in the production of neurotransmitters including tyrosine hydroxylase and tryptophan hydroxylase, which have a role in the production of dopamine and serotonin production. However, low levels of iron can lead to low synthesis of dopamine and serotonin which further leads to depression(Etebary, Nikseresht, Sadeghipour, & Zarrindast, 2010). 19% of the women with low iron levels suffer from depression (SGh, 2015). Low iron level also causes postpartum depression within a week after delivery. Almost 19.2% women at 48-hr and 9% women at 32-week of postpartum suffer from iron deficiency related depression (Albacar et al. 2011). About 37.32% of iron RDA is low in depression(Li, Wang, Xin, Song, & Zhang, 2018). Depressive symptoms can be controlled by iron supplementation as they improve neurotransmitters and iron related enzymes. Intracellular iron store depletion is also associated with depression(SGh, 2015). Low ferritin stores can cause depression not only in women but also in middle-aged men (Hidese, Saito, Asano, & Kunugi, 2018).

Iron in brain hypoxia:

Neonatal hypoxia–ischemia (HI) is the major cause of mortality in young infants and children. Free radical and reactive oxygen species play an important role in ischemic neural death. In neonatal brain, the production of superoxide and hydrogen peroxide (H_2O_2) increases and leads to hypoxia. Normally, neonates have low immunity with limited GPx activity. Neonatal brain stores more ferrous and ferric ion than that of an adult. Thus, this increases the oxidative stress on the brain especially in the hippocampus leading to cell death (Q. Lu et al. 2015).

During hypoxia, free iron accelerates the free radical formation and lipid oxidation. Transferrin–

transferrin receptor (Tf–TfR) leads to the accumulation of free iron in the brain. Ferroportin 1 (FPN1) exports the iron from a nerve cell. Hepcidin (iron regulatory hormone) which binds to FPN1, degradation of FPN1 occurs that reduces cellular iron efflux.With the passage of age. hepcidin mRNA increases in cerebral cortex, striatum and hippocampus. HIF-1 (hypoxia inducing factor 1) is activated in ischemia which induces vascular endothelial growth factor. HIF-1 is composed of HIF-1 alpha, which depends on tissue oxygen level. Thus, HIF-1 alpha induces Tf-TfR factor, which accumulates iron and leads to increase in oxidation and lipid oxidation, which eventually causes hypoxia. However, HIF-1 alpha is higher in hippocampus, cerebral cortex and striatum (Ding et al. 2011). (Figure 1)

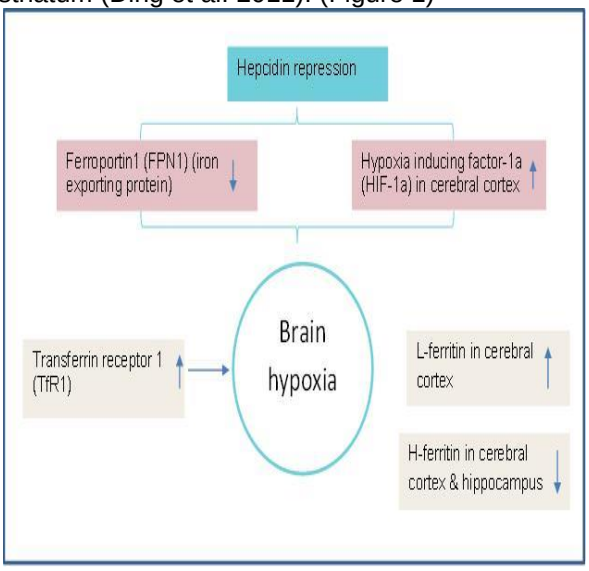

Figure 1: Mechanism of Brain Hypoxia

Zinc:

Zinc is an essential trace element that plays significant roles in various biochemical processes. It structurally forms proteins, mainly enzymes, and also mediates the immunologic and nervous system functions through the neurotransmitter signaling (Nowak, Siwek, Dudek, Ziêba, & Pilc, 2003). It also plays part in normal body functioning, such as growth and development, brain activity, immunity, and lipid metabolism (Russo, 2011a). In the body, it is found in many tissues, such as bone, skin, muscles, liver, and brain (Bitanihirwe & Cunningham, 2009). The brain, specifically hippocampus and cerebral cortex, has the highest amount of zinc (Amani, Saeidi, Nazari, & Nematpour, 2010). Zinc deficiency can either be attributed to dietary factors or genetic causes. These both factors produce similar symptoms which include diarrhea, dermatitis, alopecia, and loss of appetite. Long term deficiency impairs the growth & development, alters the learning and memory ability, and leads to altered mood, depression and behavior disorders (Gower-Winter & Levenson, 2012),(Russo, 2011a). Generally, zinc is considered safe and has less chances of causing toxicity, but, excessive accumulation can cause toxicity, that leads to increased oxidative damage, apoptosis, and excitotoxicity (Bitanihirwe & Cunningham, 2009),(Gower-Winter & Levenson, 2012),(Kambe, Tsuji, Hashimoto, & Itsumura, 2015). Therefore, a balance (called homeostasis) should be maintained by the body, to prevent deficiency or toxicity of the said element (Gower-Winter & Levenson, 2012). (Table 1)

Zinc metabolism:

Albumin and transferrin are the binding proteins that are responsible for the zinc transport in blood plasma (Osredkar & Sustar, 2011). As transferrin is also responsible for the transport of iron, the excess iron can interfere with the absorption of zinc and vice versa (Valko, Morris, & Cronin, 2005). Zinc intake does not affect the amount of zinc in plasma. Metallothioneins are the metal binding proteins responsible for the storage of zinc and copper in the body. These also modulate the zinc absorption by 15-40%. ZIP (Zrt/Irt-like protein) and ZnT (Zinc transporter) are the proteins that deal with the transportation of the zinc. Increased concentrations of copper may hinder that of the zinc, as both are absorbed by metallothioneins (Osredkar & Sustar, 2011).

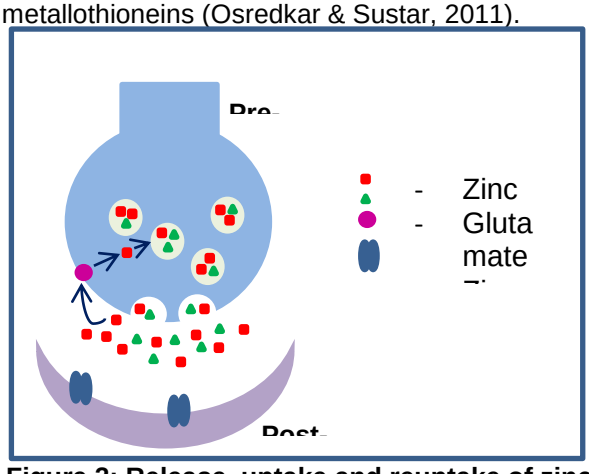

Figure 2: Release, uptake and reuptake of zinc in neurons

Zinc is stored (in high amounts) in the synaptic vesicles and in an activity dependent manner, it is released along with glutamate.

Sources of zinc:
Table 3: Zinc quantity in fruits and vegetables (mg)

Fruit And Fruit Juices:					
Name	**Quantity**	**Zinc**	**Name**	**Quantity**	**Zinc**
Apple juice	½ c	0.05	Apple slices (peeled)	½ c	0.03
Apple with peel	1	0.05	Apricot (fresh)	4 items	0.28
Avocado	½ c	0.78	Banana (fresh whole)	1 item	0.17
Blackberries (raw)	½ c	0.38	Blueberries (raw)	½ c	0.12
Cherries (sweet, raw)	½ c	0.05	Cranberries (raw)	½ c	0.05
Dates (whole)	¼ c	0.12	Figs (raw, medium)	2 items	0.14
Grapefruit juice	½ c	0.08	Grapefruit raw	½ c	0.07
Grapes	½ c	0.02	Raisins, seeded	¼ c	0.07
Guava, raw	1 item	0.12	Lemon, raw	1 item	0.10
Mango	½ c	0.03	Melon	½ c	0.14
Watermelon	½ c	0.07	Orange (raw)	1 item	0.09
Orange (sections)	½ c	0.06	Papaya	½ c	0.05
Peach (raw, medium)	1 item	0.25	Pear (raw)	1 item	0.16
Pineapple (raw)	½ c	0.09	Pomegranate	1 item	0.18
Prunes, dried	2 items	0.07			
Vegetables:					
Artichoke (boiled)	1 item	0.48	Asparagus (boiled)	½ c	0.54
Beets (whole, boiled)	2 items	0.35	Broccoli (raw)	½ c	0.19
Cabbage (boiled)	1 c	0.30	Carrots (baby, raw)	8 items	0.13
Cauliflower (boiled)	½ c	0.10	Cucumber	¼ item	0.14
Lettuce	11 items	0.16	Spinach (chopped, boiled)	½ c	0.68
Okra (boiled)	½ c	0.34	Tomato (fresh)	1 item	0.20
Onion (chopped, boiled)	½ c	0.21	Turnips (chopped, boiled)	½ c	0.10
Watercress	1	0.03			

Reference: Understanding Nutrition by Whitney Rolfe's (12th Edition) - Appendix H (H-14 – H-29)

The presynaptic stimulation of the neuron causes the zinc to be released in the synapse, from where its uptake into the postsynaptic neuron takes place through gated zinc channels (Fukada, Yamasaki, Nishida, Murakami, & Hirano, 2011). (**Error! Reference source not found.**)

Zinc and internalizing behavior:

Internalizing behaviors include depression, anxiety, and withdrawal (Bauminger, Solomon, & Rogers, 2010).

Depression:

The effect of various nutrients (for example: magnesium) in causation of depression has been studied but the effect of zinc intake has not been in the limelight. This relationship has been focused since few years and so a number of studies were conducted to examine it (Yary & Aazami, 2012). A number of studies have shown that in major depression, the levels of zinc in blood (either serum or plasma) are reduced (or low) (Nowak, et al. 2003). Similarly, in humans (adults) and animals, the low levels of zinc have been related to depression symptoms (DiGirolamo et al. 2010),(Sowa-Kućma et al. 2008). For animals and humans (young children), anxiety and zinc concentrations are inversely related to each other (Hubbs-Tait, Kennedy, Droke, Belanger, & Parker, 2007),(Takeda, Tamano, Kan, Itoh, & Oku, 2007),(Sawada & Yokoi, 2010),(Grønli, Kvamme, Friborg, & Wynn, 2013). A beneficial effect of zinc supplementation in antidepressant therapy for unipolar depression is concluded through experiments (Nowak, et al. 2003). A combination of ineffective, low zinc doses and that of citalopram and imipramine reduced the depression in rats forced swim test (Kroczka, Branski, Palucha, Pilc, & Nowak, 2001),(Szewczyk et al. 2002). In rats, a significant antidepressant result was produced due to the administration of zinc (300mg/L) added in drinking water po (per os-by mouth) for more than 30 days (Franco et al. 2008).

Anxiety:

Due to the probable association between zinc and neurologic disorders, a number of experiments have been conducted to clarify this relationship (Russo, 2011b).In young rats, deprivation of zinc resulted in an increase in

anxiety like behavior. This might be attributed to the increase in size of adrenal gland, due to zinc deficiency. As corticosterone is released form the adrenal gland, 22 days zinc deficiency resulted in a marked rise in its serum concentration (Chu, Mouat, Harris, Coffield, & Grider, 2003). This concentration rise of serum corticosterone cannot be regarded to the low levels of zinc in serum. Anorexia is also an effect of zinc deficiency, thus severe deprivation of food can be associated with the rise in corticosterone (Takeda, et al. 2007). This rise causes a rise in the concentration, in extracellular fluid of brain (Cook, 2002). In rodents, the zinc administration (15 and 20mg/kg dose) for 1 week, determined the role of zinc in anxiety (Joshi, Akhtar, Najmi, Khuroo, & Goswami, 2012). Blood analysis of individuals suffering from anxiety revealed plasma levels of low zinc, high copper, and high Zn-Cu ratio in plasma. When 20 out of 38 participants were given supplementation (vitamin B_6 and zinc) diet, their plasma levels returned to normal and symptoms of anxiety improved notably (Russo, 2011b). Experiment conducted on women, to assess the effect of zinc and magnesium on postpartum depression and anxiety, concluded that Zn and Mg supplementation did not help in improving the symptoms (Fard et al. 2017). In preschoolers, studies have suggested that low levels of zinc are linked with the increased behavior problems (including depression, anxiety, aggression etc.) (Liu et al. 2014).

Mechanism (depression and anxiety):

According to several studies, the pathophysiology and psychotherapy of depression is credited to the alteration in the expression of BDNF (brain derived neurotropic factor) gene (Chen, Dowlatshahi, MacQueen, Wang, & Young, 2001). Generally, there is a reduction in the expression of BDNF, whereas, antidepressants act to increase this factor (Castren, 2004),(Chen, et al. 2001),(Sowa-Kućma, et al. 2008). Various clinical trials have concluded that the blood of depressed patients has low levels of BDNF (Karege et al. 2002),(Shimizu et al. 2003). In rats, zinc administration(in the form of zinc aspartate), for 7, 14, and 35 days, resulted in an increase in BDNF mRNA (hippocampus) by 17-39%, whereas 100% rise in BDNF mRNA (cortisol) with just 35 days of exposure (Sowa-Kućma, et al. 2008). Various effective antidepressants act to impede the activity of NMDA (N-methyl D-aspartate) receptor by enhancing the activity of BDNF (Sowa-Kućma, et al., 2008). The Zn ion functions (just as antidepressants (Sowa-Kućma, et al., 2008)) antagonistically to NMDA to reduce anxiety, depression, and psychosis (Joshi, et al., 2012). The overall correlation between NMDA receptor and BDNF needs to be considered. Under normal body conditions the activity of NMDA receptor is increased by BDNF (Caldeira et al. 2007),(Xu et al. 2006). Under abnormal conditions (such as stress) this association might be changed (Sowa-Kućma, et al. 2008). BDNF may act to improve and retard the activity of NMDA receptor through TrkB and p75NTR receptors, respectively (Crozier, Bi, Han, & Plummer, 2008). The prolonged exposure to BDNF suppresses the TrkB receptor, resulting in decreased activity of NMDA. This mechanism might possibly explain the increased expression of BDNF associated with the decreased activity of NMDA receptor, resulting from prolonged use of antidepressants. So, zinc functions like antidepressants, as the expression of BDNF is enhanced whereas NMDA receptor is suppressed (Sowa-Kućma, et al. 2008). GABA (gamma aminobutyric acid) and glutamate also play important function in mood disorders, specifically depression and anxiety. Zinc is linked with GABA and glutamate, as it functions to impair the GABA activity in anxiety (Russo, 2011b).

Zinc and externalizing behavior:

Externalizing behaviors include aggression, impulsiveness, and conduct and control problems (Bauminger, et al. 2010).

The levels of zinc are linked with a number of behaviors, this association has been studied through different experiments (Oner et al. 2010). In ADHD, all the scores on Conner's subscale were improved due to the zinc supplementation (El-Bakry et al. 2019). The lead exposure is found to be associated with the development of conduct disorders (Braun et al.2008) and violent activity (criminal like) in children and young adults, respectively (Wright et al. 2008). These behavioral disorders were improved as a result of zinc supplementation, thus confirming the association between zinc and behavioral activity (Ademuyiwa, Agarwal, Chandra, & Behari, 2010). A study conducted in Iraq, on primary school children, revealed that the aggressive children had reduced levels of zinc in the saliva (Jwad & Abd, 2016). Low levels of zinc in serum are thought to be associated with aggression (Joe et al. 2018). In young males, micronutrient therapy was seen to be effective against violence and aggression (Hambly et al. 2017). In dogs, supplementation

with Zn, Mg, and Ω-3 fatty acids had an effect on fear and destructive behavior. Whereas no effect was seen on the aggression of the animal (Niyyat, Azizzadeh, & Khoshnegah, 2018). Healthy male and female rats were studied for the effect of supplementation on different behaviors. This study concluded an unusual effect as the results were categorized according to the sex. Supplementation reduced the aggression in male rats, whereas had an enhancing effect in female rats (Dymond, 2011). For antisocial behavior, the risk (in later life) is increased when the diet is compromised during early life (Jackson, 2016).

Abnormality of behavior is associated with an increased level of glucocorticoids, instead of low levels of zinc in the brain, which are a result of high glucocorticoid levels. These affect the activity of hippocampus causing abnormal behavior development, including aggression (Takeda, Tamano, Nishio, & Murakami, 2016). The progression of ADHD and its associated psychological disorders (hyperactivity, conduct disorder, aggression) may be attributed to the reduced activity of BDNF. Zinc supplementation improves the impression of BDNF and so different disorders are alleviated (Tsai, 2017).

Learning and memory:

The exact role of zinc in learning and memory is still under study but many animal based experiments have suggested its important function in brain activity. The dietary deficiency of zinc has been associated with an impaired memory, in mammals (Mott & Dingledine, 2011),(Takeda, Kanno, Sakurada, Ando, & Oku, 2008). Hippocampus has the highest amount of zinc in the brain. It plays significant role in learning and memory. In hippocampus, the zinc released from the synaptic vesicles is responsible for inducing long term potentiation (Gao et al. 2011). In mouse, the long term administration of severe zinc deficient diet for five months caused an increase in apoptosis and decreased neurogenesis. Thus, confirming the link of zinc deficiency with reduced plasticity in hippocampus (Gao et al. 2009). In rats, the neurotoxic effects of aluminum were antagonized through zinc supplementation. This can be attributed to its anti-oxidative role and its ability to normalize the enzymes influenced by aluminum(H. Lu et al. 2013). The pathophysiology of Alzheimer's disease can be regarded to the deranged (either increased or decreased) values of zinc (Szewczyk, 2013). In pregnant rats, the deficiency of zinc (through the period of last trimester and that of lactation) caused an impairment of the memory and spatial learning and also negatively affected the motor activity of the offspring. Whereas, these negative effects were reversed by zinc supplementation, except for the motor activity (NAGHDI et al. 2015).

Mechanism:

The exact mechanism for impaired learning and memory due to zinc deficiency is not clearly known, but experimental studies have revealed some possible underlying mechanisms (Gao, et al. 2011). In mice, the inhibition of ZnT3 (zinc transporter-3), reduced the amount of zinc uptake in vesicle and its release in the synapse. ZnT3 is responsible for causing the uptake of zinc in synaptic vesicles. The inhibition of this transporter results in its decreased function. But, even though the amount of zinc is dropped, no impairment in learning or memory was recorded (Mott & Dingledine, 2011),(Cole, Martyanova, & Palmiter, 2001). The results of such previous studies were reconsidered and it was concluded that zinc does not affect the innate fear but does influence the associative fear, memory as well as extinction(Martel, Hevi, Friebely, Baybutt, & Shumyatsky, 2010). In six months old ZnT3 KO mice, the inactivity of ZnT3 decreases the amount of Zn. This reduction leads to the loss of cognitive function (impaired memory), characteristic feature of Alzheimer's disease (Adlard, Parncutt, Finkelstein, & Bush, 2010). The inhibition of ZnT3 also retards the signaling of Erk1/2 MAPK, which results in impaired memory (Sindreu, Palmiter, & Storm, 2011),(Jiang et al. 2011). The essential signaling molecules (such as CAM, CAMKII, CREB proteins) are negatively affected due to the deficiency of zinc, ultimately affecting the long term potentiation in the hippocampus (Gao, et al., 2011). In mice, zinc supplementation (of high doses) results in the deficiency of zinc in hippocampus, ultimately affecting learning and memory. This might be attributed to reduced amount of zinc released from synaptic vesicles and decreased activity of BDNF (Yang et al. 2013).provide all references as per journal style(Gao et al. 2011)

CONCLUSION

Iron and zinc play various significant roles in the brain activity and function. Neurological disorders, such as Alzheimer's and Parkinson's disease can be attributed to iron deficiency. Secondly, the function of iron and zinc in behavior, learning and memory has also been

established.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

AUTHOR CONTRIBUTIONS

All authors read and approved the final version.

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