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"A Study of the Relation between Iron Status and Brain Function in Experimental Animals"

Thesis Submitted by

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List of Abbreviations

AD	:	Alzheimer's disease
BBB	:	Blood-brain barrier
BCB	:	Blood-cerebrospinal fluid barrier
BER	:	Base excision repair
CA1	:	Cornu Ammonis area 1
CN	:	Control normal group
CNS	:	Central nervous system
COMT	:	Catechol O-methyl-transferase
CSF	:	Cerebrospinal fluid
DA	:	Dopamine
DMT	:	Divalent metal transporter
DMT1	:	Divalent metal transporter 1
EDTA	:	Ethylene-Diamine Tetra-Acetic acid
ELISA	:	Enzyme-linked immunosorbent assay
FBN	:	Ferroportin
FtMt	:	intramitochondrial ferritin
GABA	:	Gamma-aminobutyric acid
HCP	:	Heme carrier protein
HP	:	Hippocampus
IA	:	Iron accumulation
ID	:	Iron deficiency
iDNA	:	Iron deficiency without anaemia
IL	:	Iron-overload
IRE	:	Iron Response Element
IRPs	:	Iron regulatory proteins
L-DOPA	:	L-dihydroxyphenylalanine
Lfr	:	Lactotransferrin receptor
MAO	:	Monoamine oxidase
MCH	:	Mean corpuscular hemoglobin
MCHC	:	Corpuscular hemoglobin concentration
MCV	:	Mean corpuscular volume
mPTP	:	Mitochondrial permeability transition pore

List of Abbreviations (Cont.)

MRI	:	Magnetic resonance imaging
MTP1	:	Metal transporter 1
NBIA	:	Neurodegeneration with brain Fe accumulation
NIBSC	:	National Institute for Biological Standards and Control
OS	:	Oxidative stress
PD	:	Parkinson's disease
PEG	:	Polyethylene Glycol
PFC	:	Prefrontal cortex
PKA	:	Protein kinase A
PMSF	:	Phenylmethylsulphonyl fluoride
PP2A	:	protein phosphatase 2A
ROS	:	Reactive oxygen species
TfR	:	Transferrin receptors
TH	:	Tyrosine hydroxylase
TIBC	:	Total iron binding capacity
TMB	:	Tetra-methyl Benzidine
USRDA	:	U.S. Recommended Daily Allowance
WHO	:	World Health Organization
β-TT	:	β-thalassemia trait

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Abstract

Iron is the most important element in the body, essential for almost all types of cells, including brain cells. Iron deficiency in children is associated with retardation in growth and cognitive development, and the effects on cognition may be irreversible, even with treatment. Excess iron has also been associated with neurological disease, especially in reference to the increased iron content in the brains of Alzheimer's disease and parkinson's disease patients. This study was designed to evaluate the effects of dietary iron deficiency and iron load on brain function. We conducted two studies on animal and human to determine the effect of iron status on brain iron, total iron binding capacity, ferritin, transferrin, transferrin saturation, dopamine and serotonin.

In animal study, sixty three male weanling albino rats Sprague-Dawely strain were assigned to one of seven dietary treatments. Groups (1 and 2): iron-adequate groups, control normal (CN), rats were fed on the basal balanced diet containing 35 mg Fe/kg diet for 21 and 28 days, respectively. Groups (3 and 4): iron-deficient groups (ID), rats were fed on the basal diet modified to contain 3 mg Fe/kg diet for 21 and 28 days, respectively. Group (5): iron-repletion group (Repl.), rats were fed on the iron-deficient (ID) diet for 21 days followed by an iron-adequate, control normal (CN) diet for one week. Groups (6 and 7): iron-load groups (IL), rats were fed on the basal diet modified to contain 250 mg Fe/kg diet for 21 and 28 days, respectively.

Data showed that, dietary iron deficiency led to significant decrease in the levels of iron, ferritin, and % of transferrin saturation and significant increase in the TIBC and transferrin in the serum and brain of iron-deficient rats as compared to iron-adequate rats (control). Moreover, iron deficiency produced significant decrease in the measured hematological indices. On the other hand, the levels of serotonin and dopamine in the brain of iron-deficient rats were significantly decreased. Levels of iron, ferritin and % of transferrin saturation in the serum and brain tended to be greater for the iron-load rats than control normal rats, however, TIBC and transferrin exhibited the opposite trend. Hemoglobin, hematocrit and red blood cells count and hematological indices rapidly returned to be near the normal in the rats that were iron-deficient for 3 weeks and subsequently repleted with iron for one week. Results also suggest that, iron-repletion for one week in the iron-deficient rats may help reduce the deleterious effects due to iron deficiency for 3 weeks through increased iron, ferritin, and % of

transferrin saturation levels and decreased TIBC and transferrin levels in the serum and brain, as well as, increased brain serotonin and dopamine levels as compared to iron-deficient rats.

In human study, a total number of twenty seven Egyptian male children with an age range of 7-15 years, the chosen cases included three groups. Control normal group (CN): hemoglobin, 11-12.8 g/dl (Group 1). Iron- deficient group (ID): hemoglobin, 8-9.5 g/dl (Group 2). Iron-overload group (IL): hemoglobin, 6-8 g/dl (thalassemic group) (Group 3). Studies in human with iron deficiency anaemia or iron overload thalassemia revealed significant decrease in the hematological parameters (hemoglobin, hematocrit and red blood cells count) when compared to control group. Results showed that iron deficiency anaemia significantly increased red blood cell indices, serum TIBC and transferrin and significantly decreased serum iron content, % of transferrin saturation, serotonin and dopamine and non-significantly decreased serum ferritin levels. A significant increase in the serum iron content, ferritin, % of transferrin saturation, serotonin and dopamine, while a significant decrease in serum TIBC and transferrin levels were observed in the iron-overload thalassemic childerns as compared with the levels recorded in the control group.

It was concluded that iron status largely affect brain iron, ferritin, transferrin, transferrin saturation, serotonin and dopamine especially in early life. Therefore, iron is essential for normal brain function and development.

Key words: *iron deficiency • iron load • brain iron • serotonin • dopamine • rats • humans*